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(54) **IMMUNE RESPONSE INDUCER**

(57) An immunity-inducing agent comprising as an effective ingredient a specific polypeptide is disclosed. These polypeptides were isolated, by the SEREX method using a cDNA library derived from canine testis and serum from a cancer-bearing dog, as a polypeptide which binds to an antibody existing specifically in serum derived

from a cancer-bearing living body. The polypeptides can induce immunity in a living body and cause regression of a tumor in a cancer-bearing living body. Therefore, these polypeptides are especially effective as a therapeutic and/or prophylactic agent for a cancer(s).

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Description

TECHNICAL FIELD

- 5 **[0001]** The present invention relates to a novel immunity-inducing agent useful as a therapeutic and/or prophylactic agent for a cancer(s).

BACKGROUND ART

- 10 **[0002]** Cancers are the commonest cause for death among all of the causes for death, and the therapies therefor are mainly surgical treatment in combination with radiotherapy and chemotherapy. In spite of the developments of new surgical methods and discovery of new anti-cancer agents in recent years, treatment results of cancers are not improved very much at present except for some cancers. In recent years, by virtue of the development in molecular biology and cancer immunology, cancer antigens recognized by cytotoxic T cells reactive with cancers, as well as the genes encoding the cancer antigens, were identified, and expectations for antigen-specific immunotherapies have been raised (see Non-patent Literature 1). In immunotherapy, to reduce side effects, it is necessary that the peptide or protein recognized as the antigen exist hardly in normal cells and exist specifically in cancer cells. In 1991, Boon *et al.* of Ludwig Institute in Belgium isolated human melanoma antigen MAGE 1 recognized by CD8-positive T cells by a cDNA-expression cloning method using an autologous cancer cell line and cancer-reactive T cells (see Non-patent Literature 2). Thereafter, the SEREX (serological identifications of antigens by recombinant expression cloning) method, wherein tumor antigens recognized by antibodies produced in the living body of a cancer patient in response to the cancer of the patient himself are identified by application of a gene expression cloning method, was reported (Non-patent Literature 3; Patent Literature 1), and various cancer antigens have been isolated (see Non-patent Literatures 4 to 9). Using a part thereof as targets, clinical tests for cancer immunotherapy have started.

- 25 **[0003]** On the other hand, as in human, a number of tumors such as mammary gland tumor and squamous cell carcinoma are known in dogs and cats, and they rank high also in the statistics of diseases in dogs and cats. However, at present, no therapeutic, prophylactic or diagnostic agents exist which are effective for cancers in dogs and cats. Most of tumors in dogs and cats are realized by owners only after they advance to grow bigger, and in many cases, it is already too late to visit a hospital to receive surgical excision of the tumor or administration of a human drug (an anticancer preparation or the like), so that those dogs and cats die shortly after the treatment. Under such circumstances, if therapeutic agents, prophylactic agents and diagnostic agents for cancers effective for dogs and cats become available, their uses for canine cancers are expected to be developed.

[0004] Patent Literature 1: US 5698396 B

- 35 Non-patent Literature 1: Tsuyoshi Akiyoshi, Cancer and Chemotherapy, 24, 551-519 (1997)
 Non-patent Literature 2: Bruggen P. et al., Science, 254:1643-1647 (1991)
 Non-patent Literature 3: Proc. Natl. Acad. Sci. USA, 92:11810-11813 (1995)
 Non-patent Literature 4: Int. J. Cancer, 72:965-971 (1997)
 Non-patent Literature 5: Cancer Res., 58:1034-1041 (1998)
 40 Non-patent Literature 6: Int. J. Cancer, 29:652-658 (1998)
 Non-patent Literature 7: Int. J. Oncol., 14:703-708 (1999)
 Non-patent Literature 8: Cancer Res., 56:4766-4772 (1996)
 Non-patent Literature 9: Hum. Mol. Genet 6:33-39, 1997
 Non-patent Literature 10: Naokazu Inoue, Ryo Yamaguchi and Masahito Ikawa, Protein, Nucleic Acid and Enzyme, Vol. 50, No. 11, 1405-1412
 45 Non-patent Literature 11: J Cell Sci. 115:1825-35
 Non-patent Literature 12: Blood. 95:1788-96
 Non-patent Literature 13: Mol Endocrinol. 9:243-54 (1995)
 Non-patent Literature 14: J Cell Biol. 145 : 83-98 (1999)

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

- 55 **[0005]** An object of the present invention is to provide a novel immunity-inducing agent which is useful as a therapeutic and/or prophylactic agent for a cancer(s)

MEANS FOR SOLVING THE PROBLEMS

[0006] The present inventors intensively studied to obtain a cDNA encoding a protein which binds to an antibody existing in serum derived from a cancer-bearing living body by the SEREX method using a cDNA library derived from canine testis and serum of a cancer-bearing dog, which cDNA was used to prepare a polypeptide having the amino acid sequence shown in SEQ ID NO:2, a canine calmeglin protein having the amino acid sequence shown in SEQ ID NO:16, a canine centrosomal protein (which may be hereinafter abbreviated as CEP) having the amino acid sequence shown in SEQ ID NO:26, and the canine thyroid hormone receptor interactor 11 (which may be hereinafter described as "TRIP11") having the amino acid sequence shown in SEQ ID NO:39. Further, based on a registered canine gene having a high homology to the canine CEP of the above-described SEQ ID NO:26, a canine CEP having the amino acid sequence shown in SEQ ID NO:28 was prepared. Further, based on a human gene homologous to the obtained gene, a polypeptide having the amino acid sequence shown in SEQ ID NO:4, a human calmeglin protein having the amino acid sequence shown in SEQ ID NO:18, a human CEP having the amino acid sequence shown in SEQ ID NO:30, and a human TRIP11 having the amino acid sequence shown in SEQ ID NO:41 were prepared. The inventors then discovered that these polypeptides can induce immunocytes in a living body and cause regression of an already occurred tumor when administered to the living body, thereby completing the present invention.

[0007] That is, the present invention provides an immunity-inducing agent comprising as an effective ingredient any one of the polypeptides (a) to (c) below, the polypeptide having an immunity-inducing activity, or as an effective ingredient a recombinant vector which comprises a polynucleotide encoding the polypeptide and is capable of expressing the polypeptide *in vivo*: (a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING; (b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and (c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof. The present invention also provides a method for inducing immunity, the method comprising administering to an individual an effective amount of any one of the above-described polypeptides (a) to (c), the polypeptide having an immunity-inducing activity, or an effective amount of a recombinant vector which comprises a polynucleotide encoding the polypeptide and is capable of expressing the polypeptide *in vivo*. The present invention further provides a method for treating antigen-presenting cells, the method comprising bringing any one of the above-described polypeptides (a) to (c), the polypeptide having an immunity-inducing activity, into contact with antigen-presenting cells. The present invention further provides use of any one of the above-described polypeptides (a) to (c), the polypeptide having an immunity-inducing activity, or a recombinant vector which comprises a polynucleotide encoding the polypeptide and is capable of expressing the polypeptide *in vivo*, for production of an immunity-inducing agent.

EFFECT OF THE INVENTION

[0008] By the present invention, a novel immunity-inducing agent useful as a therapeutic and/or prophylactic agent for a cancer(s) was provided. As indicated in the Examples below, the polypeptide used in the present invention can induce immunocytes in a cancer-bearing dog and also can cause reduction or regression of an already occurred tumor when administered to a cancer-bearing dog. Therefore, the polypeptide is useful for therapy and prophylaxis of a cancer(s).

BRIEF DESCRIPTION OF THE DRAWINGS

[0009]

Fig. 1 shows the expression pattern of the gene identified in Example A-1 in normal tissues and tumor cell lines. Reference numeral 1: the expression pattern of the identified gene; Reference numeral 2: the expression pattern of the *GAPDH* gene.

Fig. 2 shows the detection by Coomassie staining of the canine-derived protein produced in *E. coli* and purified in Example A, which protein was identified in the present invention. Reference numeral 3: the band for the canine-derived protein of the present invention.

Fig. 3 shows the expression pattern of the calmeglin gene identified in the present invention in normal tissues and tumor cell lines. Reference numeral 1: the expression pattern of the calmeglin gene; Reference numeral 2: the expression pattern of the *GAPDH* gene.

Fig. 4 shows the detection by Coomassie staining of the canine calmeglin protein, which is an example of the polypeptide used in the present invention, produced in *E. coli* and purified in Example B. Reference numeral 3: the band for the canine calmeglin protein.

Fig. 5 shows the expression pattern of the gene encoding the CEP protein in normal tissues and tumor cell lines.

Reference numeral 1: the expression pattern of the gene encoding the CEP protein; Reference numeral 2: the expression pattern of the *GAPDH* gene.

Fig. 6 shows the detection by Coomassie staining of the canine CEP of SEQ ID NO:26, which is an example of the polypeptide used in the present invention, produced in *E. coli* and purified in Example C. Reference numeral 3: the band for the canine CEP protein.

Fig. 7 shows the expression pattern of the gene encoding the TRIP 11 protein in normal tissues and tumor cell lines. Reference numeral 1: the expression pattern of the gene encoding the TRIP11 protein; Reference numeral 2: the expression pattern of the *GAPDH* gene.

Fig. 8 shows the detection by Coomassie staining of the canine TRIP11 protein, which is one of the polypeptides used in the present invention, produced in *E. coli* and purified in Example D. Reference numeral 3: the band for the canine TRIP 11 protein.

BEST MODE FOR CARRYING OUT THE INVENTION

[0010] The polypeptides contained in the immunity-inducing agents of the present invention as effective ingredients are as follows. It should be noted that the term "polypeptide" in the present invention means a molecule formed by peptide bonding of a plurality of amino acids, and includes not only polypeptide molecules having large numbers of amino acids constituting them, but also low molecular weight molecules having small numbers of amino acids (oligopeptides) and full-length proteins. Thus, in the the present invention, proteins consisting of the full length of SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 are also included in "polypeptide".

(a) A polypeptide which consists of not less than 7 consecutive amino acids of a polypeptide having the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING and has an immunity-inducing activity.

(b) A polypeptide which has a homology of not less than 80% to the polypeptide (a), consists of not less than 7 amino acids, and has an immunity-inducing activity.

(c) A polypeptide which comprises the polypeptide (a) or (b) as a partial sequence thereof and has an immunity-inducing activity.

[0011] It should be noted that the term "having the amino acid sequence" in the present invention means that amino acid residues are aligned in that order. Accordingly, for example, "a polypeptide having the amino acid sequence shown in SEQ ID NO:2" means a polypeptide having a size of 306 amino acid residues, whose amino acid sequence is Met Ala Ala Leu ...(snip)... Ile Thr Ser Pro as shown in SEQ ID NO:2. Further, "a polypeptide having the amino acid sequence shown in SEQ ID NO:2" may be abbreviated as "a polypeptide of SEQ ID NO:2". This also applies to the term "having the base sequence".

[0012] As used herein, the term "immunity-inducing activity" means an ability to induce immunocytes which secrete cytokines such as interferon in a living body. Whether or not a polypeptide has an immunity-inducing activity can be confirmed using, for example, the known ELISPOT assay. More particularly, for example, as described in the Examples below, cells such as peripheral blood mononuclear cells are obtained from a living body to which a polypeptide whose immunity-inducing activity is to be evaluated was administered, which cells are then cocultivated with the polypeptide, followed by measuring the amount of a cytokine produced by the cells using a specific antibody, thereby measuring the number of immunocytes in the cells, which enables evaluation of the immunity-inducing activity. Further, as described in the Examples below, a recombinant polypeptide prepared based on the amino acid sequence of SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 can cause regression of a tumor by its immunity-inducing activity when administered to a cancer-bearing living body. Therefore, the above-described immunity-inducing activity can be evaluated also as the ability to inhibit the growth of cancer cells expressing the polypeptide of SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 or to cause reduction or disappearance of a cancer tissue (tumor) (hereinafter referred to as "anti-tumor activity"). The anti-tumor activity of a polypeptide can be confirmed by, for example, observation of whether or not the tumor is reduced when the polypeptide was administered to a cancer-bearing living body, as more particularly described in the Examples below. Further, the anti-tumor activity of a polypeptide can be evaluated also by observation of whether or not T cells stimulated with the polypeptide (that is, T cells brought into contact with antigen-presenting cells which present the polypeptide) show a cytotoxic activity against tumor cells *in vitro*. The contact between T cells and antigen-presenting cells can be carried out by cocultivation of the both in a liquid medium, as mentioned below. Measurement of the cytotoxic activity can be carried out by, for example, a known method called ⁵¹Cr release assay described in Int.J.Cancer,58:p317,1994. In cases where a polypeptide is used for therapy and/or prophylaxis of a cancer(s), the evaluation of the immunity-inducing activity is preferably carried out using the anti-tumor activity as an index, although the index is not restricted.

[0013] The amino acid sequence shown in SEQ ID NO:2 in SEQUENCE LISTING is the amino acid sequence of the polypeptide with unknown function isolated as a polypeptide which binds to an antibody existing specifically in serum

derived from a cancer-bearing dog, which isolation was carried out by the SEREX method using a canine testis-derived cDNA library and serum of a cancer-bearing dog (see Example A-1). It is registered in the NCBI database under Accession No. XP_535343 (protein) and Accession No. XM_535343 (coding gene), but its function has not been reported. Further, the amino acid sequence shown in SEQ ID NO:4 is an amino acid sequence of a human homologous factor of the polypeptide of SEQ ID NO:2 isolated as described above. This human homologous factor is also a protein whose function is unknown, which is registered in the NCBI database under Accession No. NP_689873 (protein) and Accession No. NM_152660 (coding gene). The homology between them is 93% in terms of base sequence and 99% in terms of amino acid sequence.

[0014] The respective amino acid sequences shown in SEQ ID NOs:16 and 18 are those of the calmegin protein isolated as a polypeptide and a human homologous factor thereof, which polypeptide binds to an antibody existing specifically in serum derived from a cancer-bearing dog, which isolation was carried out by the SEREX method using a canine testis-derived cDNA library and serum of a cancer-bearing dog (see Example B-1). Calmegin was identified as a protein which is expressed specifically at the time of differentiation of a spermatid, and it has a chaperone activity *in vitro*. Since it is expressed only in testis and disappears in a mature sperm, calmegin is considered to have a function to fold proteins involved in differentiation of spermatid (Non-patent Literature 10, Naokazu Inoue, Ryo Yamaguchi and Masahito Ikawa, Protein, Nucleic Acid and Enzyme, Vol. 50, No. 11, 1405-1412). However, there has been no report showing that the protein is expressed in a cancer and useful for therapy or prophylaxis thereof. The homology between the canine calmegin gene and the human calmegin gene is 90% in terms of base sequence and 89% in terms of amino acid sequence.

[0015] The respective amino acid sequences shown in SEQ ID NOs:26, 28 and 30 are those of the CEP isolated as a polypeptide, a canine factor having a high homology to the polypeptide and a human homologous factor of the polypeptide, which polypeptide binds to an antibody existing specifically in serum derived from a cancer-bearing dog, which isolation was carried out by the SEREX method using a canine testis-derived cDNA library and serum of a cancer-bearing dog (see Example C-1). CEP is a protein which is required by the centrosome to control microtubules and also involved in maturation of the centrosome. It is known that chromosomal translocation frequently occurs in some of myeloproliferative disorders, and since the *CEP* gene exists at the point where the translocation occurs, CEP is considered to have a certain relationship with the disorders. However, there has been no report showing that the protein is expressed in a cancer and useful for therapy or prophylaxis thereof (Non-patent Literature 11: J Cell Sci. 115:1825-35; Non-patent Literature 12: Blood. 95:1788-96). The homology between the canine *CEP* gene encoding the CEP of SEQ ID NO:26 and the human *CEP* gene is 87% in terms of base sequence and 84% in terms of amino acid sequence.

[0016] The respective amino acid sequences shown in SEQ ID NOs:39 and 41 are those of the TRIP11 protein isolated as a polypeptide and a human homologous factor thereof, which polypeptide binds to an antibody existing specifically in serum derived from a cancer-bearing dog, which isolation was carried out by the SEREX method using a canine testis-derived cDNA library and serum of a cancer-bearing dog (see Example D-1). TRIP11 (thyroid hormone receptor interactor 11) was first identified as a factor which interacts with the thyroid hormone receptor β , and its binding to Golgi bodies and microtubules also became evident, so that TRIP11 is considered to play a role in maintaining the shapes of these organelles. However, there has been no report showing that the protein is expressed in a cancer and useful for therapy or prophylaxis thereof (Non-patent Literature 13, Mol Endocrinol. 9:243-54 (1995); Non-patent Literature 14, J Cell Biol. 145: 83-98 (1999)). The homology between the canine *TRIP11* gene and the human *TRIP11* gene is 88% in terms of base sequence and 86% in terms of amino acid sequence.

[0017] The polypeptide (a) consists of not less than 7 consecutive, preferably not less than 9 consecutive amino acids of a polypeptide having the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41, and has an immunity-inducing activity. The polypeptide especially preferably has the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41. As known in the art, a polypeptide consists of not less than about 7 amino acid residues can exert its antigenicity. Thus, a polypeptide consists of not less than 7 consecutive amino acid residues of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 can have an immunity-inducing activity, so that it can be used for preparation of the immunity-inducing agent of the present invention. However, in view of the fact that antibodies produced against antigenic substances in a living body are polyclonal antibodies, it is thought that an antigenic substance composed of larger number of amino acid residues can induce more types of antibodies which can recognize various sites on the antigenic substance, thereby attaining higher immunity-inducing activity. Therefore, in order to increase the immunity-inducing activity, in the case of SEQ ID NO:2 or 4, the number of the amino acid residues may be preferably not less than 30, more preferably not less than 100, still more preferably not less than 200, still more preferably not less than 250. In the case of SEQ ID NO:16 or 18, the number of the amino acid residues may be preferably not less than 30, more preferably not less than 100, still more preferably not less than 200, still more preferably not less than 300, still more preferably not less than 400, still more preferably not less than 550. In the case of SEQ ID NO:26, 28 or 30, the number of the amino acid residues may be preferably not less than 30, more preferably not less than 100, still more preferably not less than 300, still more preferably not less than 600, still more preferably not less than 1000, still more preferably not less than 1500, still more preferably not less than 2000. In the case of SEQ ID NO:39 or 41, the number of the amino acid residues may

be preferably not less than 30, more preferably not less than 100, still more preferably not less than 300, still more preferably not less than 600, still more preferably not less than 1000, still more preferably not less than 1500.

[0018] As a principle of immune induction by administration of a cancer antigenic polypeptide, the following process is known: the polypeptide is incorporated into an antigen-presenting cell and then degraded into smaller fragments by peptidases in the cell, followed by presentation of the fragments on the surface of the cell. The fragments are then recognized by a cytotoxic T cell or the like, which selectively kills cells presenting the antigen.

[0019] The size of the polypeptide presented on the surface of the antigen-presenting cell is relatively small and about 7 to 30 amino acids. Therefore, from the view point of presenting thereof on the surface of the antigen-presenting cell, a polypeptide consisting of about 7 to 30, preferably about 9 to 30 consecutive amino acids of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 is sufficient as the above-described polypeptide (a). In some cases, these relatively small polypeptides are presented directly on the surface of the antigen-presenting cells without incorporation thereof into the antigen-presenting cells.

[0020] However, as described above, since a polypeptide incorporated into an antigen-presenting cell is cleaved at random sites by peptidases in the cell to yield various polypeptide fragments, which are then presented on the surface of the antigen-presenting cell, administration of a large polypeptide such as the entire region of SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 inevitably causes production of polypeptide fragments by degradation thereof in the antigen-presenting cell, which fragments are effective for immune induction via the antigen-presenting cell. Therefore, for immune induction via antigen-presenting cells, a large polypeptide can also be preferably used. In the case of SEQ ID NO:2 or 4, the number of the amino acids may be preferably not less than 30, more preferably not less than 100, still more preferably not less than 200, still more preferably not less than 250. In the case of SEQ ID NO:16 or 18, the number of the amino acids may be preferably not less than 30, more preferably not less than 100, still more preferably not less than 200, still more preferably not less than 400, still more preferably not less than 550. In the case of SEQ ID NO:26, 28 or 30, the number of the amino acids may be preferably not less than 30, more preferably not less than 100, still more preferably not less than 300, still more preferably not less than 600, still more preferably not less than 1000, still more preferably not less than 1500, still more preferably not less than 2000. In the case of SEQ ID NO:39 or 41, the number of the amino acids may be preferably not less than 30, more preferably not less than 100, still more preferably not less than 300, still more preferably not less than 600, still more preferably not less than 1000, still more preferably not less than 1500.

[0021] The above-described polypeptide (b) is the same polypeptide as the above-described polypeptide (a) except that a small number of amino acid residues are substituted, deleted and/or inserted, which has a homology of not less than 80%, preferably not less than 90%, more preferably not less than 95%, still more preferably not less than 98% to the original sequence, and has an immunity-inducing activity. It is well known in the art that, in general, there are cases where a protein antigen retains substantially the same antigenicity as the original even if the amino acid sequence of the protein is modified such that a small number of amino acids are substituted, deleted and/or inserted. Therefore, since the above-described polypeptide (b) may also exert an immunity-inducing activity, it can be used for preparation of the immunity-inducing agent of the present invention. Further, the above-described polypeptide (b) is also preferably the same polypeptide as one having the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 except that one or several amino acid residues are substituted, deleted and/or inserted.

[0022] As used herein, the term "homology" of amino acid sequences means a value expressed in percentage which is calculated by aligning two amino acid sequences to be compared such that the number of matched amino acid residues is the maximum, and dividing the number of the matched amino acid residues by the number of the total amino acid residues. When the above-described alignment is carried out, a gap(s) is/are inserted into one or both of the two sequences to be compared as required. Such alignment of sequences can be carried out using a well-known program such as BLAST, FASTA or CLUSTAL W. When a gap(s) is/are inserted, the above-described number of the total amino acid residues is calculated by counting one gap as one amino acid residue. When the thus counted numbers of the total amino acid residues are different between the two sequences to be compared, the homology (%) is calculated by dividing the number of matched amino acid residues by the number of the total amino acid residues in the longer sequence.

[0023] The 20 types of amino acids constituting the naturally occurring proteins may be classified into groups each of which has similar properties, for example, into neutral amino acids with side chains having low polarity (Gly, Ile, Val, Leu, Ala, Met, Pro), neutral amino acids having hydrophilic side chains (Asn, Gln, Thr, Ser, Tyr, Cys), acidic amino acids (Asp, Glu), basic amino acids (Arg, Lys, His) and aromatic amino acids (Phe, Tyr, Trp). It is known that, in most cases, substitutions of amino acids within the same group do not change the properties of the polypeptide. Therefore, in cases where amino acid residue(s) in the above described polypeptide (a) in the present invention is/are substituted, the probability that the immunity-inducing activity can be maintained may be made high by conducting the substitution(s) within the same group.

[0024] The above-described polypeptide (c) comprises the above-described polypeptide (a) or (b) as a partial sequence and has an immunity-inducing activity. That is, the polypeptide (c) has another/other amino acid(s) or polypeptide(s) added at one or both ends of the polypeptide (a) or (b), and has an immunity-inducing activity. Such a polypeptide can also be used for preparation of the immunity-inducing agent of the present invention.

[0025] For example, the above-described polypeptides can be synthesized by a chemical synthesis method such as the Fmoc method (fluorenylmethylcarbonyl method) or the tBoc method (*t*-butoxycarbonyl method). Further, they can be synthesized by conventional methods using various commercially available peptide synthesizers. Further, the polypeptide of interest can be obtained by a known genetic engineering method wherein a polynucleotide encoding the above-described polypeptide is prepared and incorporated into an expression vector, which is then introduced into a host cell, in which the polypeptide is produced.

[0026] The polynucleotide encoding the above-described polypeptide can be easily prepared by a known genetic engineering method or a conventional method using a commercially available nucleic acid synthesizer. For example, DNA having the base sequence of SEQ ID NO:1, 15, 25, 27 or 38 can be prepared by carrying out PCR using the chromosomal DNA or a cDNA library of a dog as a template and using a pair of primers designed such that the primers can amplify the base sequence described in SEQ ID NO:1, 15, 25, 27 or 38, respectively. DNA having the base sequence of SEQ ID NO:3, 17, 29 or 40 can be prepared similarly by using as the above-described template the human chromosomal DNA or a cDNA library. Conditions for the PCR reaction can be selected as appropriate, and examples of the conditions include, but are not limited to, those wherein a cycle comprising the reaction steps of 94°C for 30 seconds (denaturing), 55°C for 30 seconds to 1 minute (annealing), and 72°C for 2 minutes (extension) is repeated, for example, 30 times, followed by allowing the reaction to proceed at 72°C for 7 minutes. Further, a desired DNA can be isolated by preparing an appropriate probe or primer based on the information of the base sequence and the amino acid sequence shown in SEQ ID NOs:1 to 4, 15 to 18, 25 to 30, 38 to 41 in SEQUENCE LISTING of the present specification and then using the probe or primer for screening of a cDNA library from a dog or a human. The cDNA library is preferably prepared from cells, an organ or a tissue expressing the protein of SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41. Operations such as the above-described preparation of a probe or a primer, construction of a cDNA library, screening of a cDNA library and cloning of a gene of interest are known to those skilled in the art, and can be carried out according to, for example, Molecular Cloning, 2nd Ed. or Current Protocols in Molecular Biology. From the thus obtained DNA, DNA encoding the above-described polypeptide (a) can be obtained. Further, since codons encoding each amino acid are known, the base sequence of a polynucleotide encoding a specific amino acid sequence can be easily specified. Therefore, the base sequences of polynucleotides encoding the above-described polypeptide (b) and polypeptide (c) can also be easily specified, so that such polynucleotides can also be easily synthesized using a commercially available nucleic acid synthesizer according to a conventional method.

[0027] The above-described host cells are not restricted as long as they can express the above-described polypeptide, and examples thereof include, but are not limited to, prokaryotic cells such as *E. coli*; and eukaryotic cells such as mammalian cultured cells including monkey kidney cells COS 1 and Chinese hamster ovary cells CHO, budding yeast, fission yeast, silkworm cells, and *Xenopus laevis* egg cells.

[0028] In cases where prokaryotic cells are used as the host cells, an expression vector having the origin that enables its replication in a prokaryotic cell, a promoter, a ribosome binding site, a DNA cloning site, a terminator and the like is used as the expression vector. Examples of the expression vector for *E. coli* include the pUC system, pBluescript II, pET expression system and pGEX expression system. By incorporating DNA encoding the above-described polypeptide into such an expression vector and transforming prokaryotic host cells with the vector, followed by culturing the obtained transformant, the polypeptide encoded by the above-described DNA can be expressed in the prokaryotic host cells. In this case, the polypeptide can also be expressed as a fusion protein with another protein.

[0029] In cases where eukaryotic cells are used as the host cells, an expression vector for eukaryotic cells having a promoter, splicing site, poly(A) addition site and the like is used as the expression vector. Examples of such an expression vector include pKA1, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, the EBV vector, pRS, pcDNA3, pMSG and pYES2. In the same manner as described above, by incorporating DNA encoding the above-described polypeptide into such an expression vector and transforming eukaryotic host cells with the vector, followed by culturing the obtained transformant, the polypeptide encoded by the above-described DNA can be expressed in the eukaryotic host cells. In cases where pIND/V5-His, pFLAG-CMV-2, pEGFP-N1 or pEGFP-C1 was used as the expression vector, the above-described polypeptide can be expressed as a fusion protein having various added tags such as His tag, FLAG tag, myc tag, HA tag or GFP.

[0030] Introduction of the expression vector to the host cells can be carried out using a well-known method such as electroporation, the calcium phosphate method, the liposome method or the DEAE dextran method.

[0031] Isolation and purification of a polypeptide of interest from the host cells can be carried out by a combination of known separation operations. Examples of the operations include, but are not limited to, treatment by a denaturant such as urea or by a surfactant; ultrasonication treatment; enzyme digestion; salting-out and solvent fractional precipitation; dialysis; centrifugation; ultrafiltration; gel filtration; SDS-PAGE; isoelectric focusing; ion-exchange chromatography; hydrophobic chromatography; affinity chromatography; and reversed-phase chromatography.

[0032] The polypeptides obtained by the above method include, as mentioned above, those in the form of a fusion protein with another arbitrary protein. Examples thereof include fusion proteins with glutathion S-transferase (GST) and with a His tag. Such a polypeptide in the form of a fusion protein is also included within the scope of the present invention

as the above-described polypeptide (c). Further, in some cases, a polypeptide expressed in a transformed cell is modified in various ways in the cell after translation thereof. Such a polypeptide having a post-translational modification is also included within the scope of the present invention as long as it has an immunity-inducing activity. Examples of such a post-translational modification include elimination of N-terminus methionine, N-terminus acetylation, glycosylation, limited degradation by an intracellular protease, myristoylation, isoprenylation and phosphorylation.

[0033] As described concretely in the following Examples, the above-described polypeptide having an immunity-inducing activity can cause regression of an already occurred tumor when administered to a cancer-bearing living body. Therefore, the immunity-inducing agent of the present invention can be used as a therapeutic and/or prophylactic agent for a cancer(s). In this case, cancers to be treated are those expressing the gene encoding the polypeptide of SEQ ID NO:2 or 4, and examples thereof include, but are not limited to, brain tumor; squamous cell carcinomas of head, neck, lung, uterus and esophagus; melanoma; adenocarcinomas of lung, breast and uterus; renal cancer; malignant mixed tumor; hepatocellular carcinoma; basal cell carcinoma; acanthomatous epulis; intraoral tumor; perianal adenocarcinoma; anal sac tumor; anal sac apocrine carcinoma; Sertoli cell tumor; vulva cancer; sebaceous adenocarcinoma; sebaceous epithelioma; sebaceous adenoma; sweat gland carcinoma; intranasal adenocarcinoma; nasal adenocarcinoma; thyroid cancer; colon cancer; bronchial adenocarcinoma; adenocarcinoma; ductal carcinoma; mammary adenocarcinoma; combined mammary adenocarcinoma; mammary gland malignant mixed tumor; intraductal papillary adenocarcinoma; fibrosarcoma; hemangiopericytoma; osteosarcoma; chondrosarcoma; soft tissue sarcoma; histiocytic sarcoma; myxosarcoma; undifferentiated sarcoma; lung cancer; mastocytoma; cutaneous leiomyoma; intra-abdominal leiomyoma; leiomyoma; chronic lymphocytic leukemia; lymphoma; gastrointestinal lymphoma; digestive organ lymphoma; small cell or medium cell lymphoma; adrenomedullary tumor; granulosa cell tumor; pheochromocytoma; bladder cancer (transitional cell carcinoma); suppurative inflammation; intra-abdominal liver tumor; liver cancer; plasmacytoma; malignant hemangiopericytoma; angiosarcoma; anal sac adenocarcinoma; oral cancer; metastatic malignant melanoma; amelanotic malignant melanoma; cutaneous malignant melanoma; malignant myoepithelioma; malignant seminoma; seminoma; adenocarcinoma of the large intestine; gastric adenocarcinoma; low-grade sebaceous carcinoma; ceruminous adenocarcinoma; apocrine carcinoma; poorly differentiated apocrine sweat gland carcinoma; malignant fibrous histiocytoma; multiple myeloma; mesenchymal malignant tumor; liposarcoma; osteosarcoma; sarcoma of unknown origin; soft part sarcoma (spindle cell tumor); poorly differentiated sarcoma; synovial sarcoma; angiosarcoma; metastatic malignant epithelioma; tubular mammary adenocarcinoma; mammary ductal carcinoma; inflammatory breast cancer; germinoma; leukemia; invasive trichoepithelioma; medium cell lymphoma; multicentric lymphoma; osteosarcoma (mammary gland); mastocytoma (Patnaik II type); mastocytoma (Grade II); and leiomyosarcoma. The animals to be treated are mammals, especially preferably humans, dogs and cats.

[0034] The administration route of the immunity-inducing agent of the present invention to a living body may be either oral administration or parenteral administration, and is preferably parenteral administration such as intramuscular administration, subcutaneous administration, intravenous administration or intraarterial administration. In cases where the immunity-inducing agent is used for therapy of a cancer, it may be administered to a regional lymph node in the vicinity of the tumor to be treated, as described in the Examples below, in order to enhance its anticancer activity. The dose may be any dose as long as the dose is effective for immune induction, and in cases where the agent is used for therapy and/or prophylaxis of a cancer, the dose may be one effective for therapy and/or prophylaxis of the cancer. The dose effective for therapy and/or prophylaxis of a cancer is appropriately selected depending on the size of the tumor, the symptom and the like, and usually, 0.0001 μg to 1000 μg , preferably 0.001 μg to 1000 μg of the agent in terms of the effective ingredient may be administered once or in several times per day per animal to be treated. The agent is preferably administered in several times, every several days to several months. As concretely shown in the Examples below, the immunity-inducing agent of the present invention can cause regression of an already occurred tumor. Therefore, since the agent can exert its anticancer activity also against a small number of cancer cells in the early stage, development or recurrence of the cancer can be prevented by using the agent before development of a cancer or after therapy for a cancer. That is, the immunity-inducing agent of the present invention is effective for both therapy and prophylaxis of a cancer.

[0035] The immunity-inducing agent of the present invention may contain only a polypeptide or may be formulated by mixing as appropriate with an additive such as a pharmaceutically acceptable carrier, diluent or vehicle suitable for each administration mode. Formulation methods and additives which may be used are well-known in the field of formulation of pharmaceuticals, and any of the methods and additives may be used. Specific examples of the additive include, but are not limited to, diluents such as physiological buffer solutions; vehicles such as sucrose, lactose, corn starch, calcium phosphate, sorbitol and glycine; binders such as syrup, gelatin, gum arabic, sorbitol, polyvinyl chloride and tragacanth; and lubricants such as magnesium stearate, polyethylene glycol, talc and silica. Examples of the formulation include oral preparations such as tablets, capsules, granules, powders and syrups; and parenteral preparations such as inhalants, injection solutions, suppositories and solutions. These formulations may be prepared by commonly known production methods.

[0036] The immunity-inducing agent of the present invention may be used in combination with an immunoenhancer

capable of enhancing the immune response in a living body. The immunoenhancer may be contained in the immunity-inducing agent of the present invention or administered as a separate composition to a patient in combination with the immunity-inducing agent of the present invention.

[0037] Examples of the above-described immunoenhancer include adjuvants. Adjuvants can enhance the immune response by providing a reservoir of antigen (extracellularly or within macrophages), activating macrophages and stimulating specific sets of lymphocytes, thereby enhancing the anticancer activity. Therefore, especially in cases where the immunity-inducing agent of the present invention is used for therapy and/or prophylaxis of a cancer, the immunity-inducing agent preferably comprises an adjuvant, in addition to the above-described polypeptide as an effective ingredient. Many types of adjuvants are well-known in the art, and any of these adjuvants may be used. Specific examples of the adjuvants include MPL (SmithKline Beecham) and homologues of *Salmonella minnesota* Re 595 lipopolysaccharide obtained after purification and acid hydrolysis of the lipopolysaccharide; QS21 (SmithKline Beecham), pure QA-21 saponin purified from extract of *Quillja saponaria*; DQS21 described in WO96/33739 (SmithKline Beecham); QS-7, QS-17, QS-18 and QS-L1 (So and 10 others, "Molecules and cells", 1997, Vol. 7, p. 178-186); Freund's incomplete adjuvant; Freund's complete adjuvant; vitamin E; Montanide; alum; CpG oligonucleotides (see, for example, Kreig and 7 others, "Nature", Vol. 374, p. 546-549); poly-I:C and derivatives thereof (e.g., poly ICLC); and various water in oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol. Among these, Freund's incomplete adjuvant; Montanide; poly-I:C and derivatives thereof, and CpG oligonucleotides are preferred. The mixing ratio between the above-described adjuvant and polypeptide is typically about 1:10 to 10:1, preferably about 1:5 to 5:1, more preferably about 1:1. However, the adjuvant is not limited to the above-described examples, and adjuvants known in the art other than the above-described ones (for example, see Goding, "Monoclonal Antibodies: Principles and Practice", 2nd edition, 1986) may be used when the immunity-inducing agent of the present invention is administered. Preparation methods for mixtures or emulsions of a polypeptide and an adjuvant are well-known to those skilled in the art of vaccination.

[0038] Further, in addition to the above-described adjuvants, factors that stimulate the immune response of the subject may be used as the above-described immunoenhancer. For example, various cytokines having a property to stimulate lymphocytes and/or antigen-presenting cells may be used as the immunoenhancer in combination with the immunity-inducing agent of the present invention. A number of such cytokines capable of enhancing the immune response are known to those skilled in the art, and examples thereof include, but are not limited to, interleukin-12 (IL-12), GM-CSF, IL-18, interferon- α , interferon- β , interferon- ω , interferon- γ , and Flt3 ligand, which have been shown to promote the prophylactic action of vaccines. Such factors may also be used as the above-described immunoenhancer, and can be contained in the immunity-inducing agent of the present invention, or can be prepared as a separate composition to be administered to a patient in combination with the immunity-inducing agent of the present invention.

[0039] Further, by bringing the above-described polypeptide into contact with antigen-presenting cells *in vitro*, the antigen-presenting cells can be made to present the polypeptide. That is, the above-described polypeptides (a) to (c) can be used as agents for treating antigen-presenting cells. As the antigen-presenting cells, dendritic cells or B cells, which have MHC class I molecules, may preferably be employed. Various MHC class I molecules have been identified and well-known. MHC molecules in human are called HLA. Examples of HLA class I molecules include HLA-A, HLA-B and HLA-C, more specifically, HLA-A1, HLA-A0201, HLA-A0204, HLA-A0205, HLA-A0206, HLA-A0207, HLA-A11, HLA-A24, HLA-A31, HLA-A6801, HLA-B7, HLA-B8, HLA-B2705, HLA-B37, HLA-Cw0401 and HLA-Cw0602.

[0040] The dendritic cells or B cells having MHC class I molecules can be prepared from peripheral blood by a well-known method. For example, tumor-specific dendritic cells can be induced by inducing dendritic cells from bone marrow, umbilical cord blood or patient's peripheral blood using granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 (or IL-4), and then adding a tumor-related peptide to the culture system. By administering an effective amount of such dendritic cells, a response desired for therapy of a cancer can be induced. As the cells to be used, bone marrow or umbilical cord blood donated by a healthy individual, or bone marrow, peripheral blood or the like from the patient himself may be used. When autologous cells of the patient are used, high safety can be attained and serious side effects are expected to be avoided. The peripheral blood or bone marrow may be a fresh sample, cold-stored sample or frozen sample. As for the peripheral blood, whole blood may be cultured or the leukocyte components alone may be separated and cultured, and the latter is efficient and thus preferred. Further, among the leukocyte components, mononuclear cells may be separated. In cases where the cells are originated from bone marrow or umbilical cord blood, the whole cells constituting the bone marrow may be cultured, or mononuclear cells may be separated therefrom and cultured. Peripheral blood, the leukocyte components thereof and bone marrow cells contain mononuclear cells, hematopoietic stem cells and immature dendritic cells, from which dendritic cells are originated, and also CD4-positive cells and the like. As for the cytokine to be used, the production method thereof is not restricted and naturally-occurring or recombinant cytokine or the like may be employed as long as its safety and physiological activity have been confirmed. Preferably, a preparation with assured quality for medical use is used in a minimum necessary amount. The concentration of the cytokine(s) to be added is not restricted as long as the dendritic cells are induced, and usually, the total concentration of the cytokine(s) is preferably about 10 to 1000 ng/mL, more preferably about 20 to 500 ng/mL. The culture may be carried out using a well-known medium usually used for the culture of leukocytes. The culturing temperature is not restricted as long as the

proliferation of the leukocytes is attained, and about 37°C which is the body temperature of human is most preferred. The atmospheric environment during the culturing is not restricted as long as the proliferation of the leukocytes is attained, and to flow 5% CO₂ is preferred. The culturing period is not restricted as long as the necessary number of the cells is induced, and is usually 3 days to 2 weeks. As for the apparatuses used for separation and culturing of the cells, appropriate apparatuses, preferably those whose safety when applied to medical uses have been confirmed, and whose operations are stable and simple, may be employed. Particularly, as for the cell-culturing apparatus, not only the general vessels such as a Petri dish, flask and bottle, but also a layer type vessel, multistage vessel, roller bottle, spinner type bottle, bag type culturing vessel, hollow fiber column and the like may be used.

[0041] Bringing the above-described peptide of the present invention into contact with the antigen presenting cells *in vitro* may be carried out by a well-known method. For example, it may be carried out by culturing the antigen-presenting cells in a culture medium containing the above-described polypeptide. The concentration of the peptide in the medium is not restricted, and usually about 1 µg/ml to 100 µg/ml, preferably about 5 µg/ml to 20 µg/ml. The cell density during the culturing is not restricted and is usually about 10³ cells/ml to 10⁷ cells/ml, preferably about 5 × 10⁴ cells/ml to 5 × 10⁶ cells/ml. The culturing may be carried out according to a conventional method, and is preferably carried out at 37°C under atmosphere of 5% CO₂. The maximum length of the peptide which can be presented on the surface of the antigen-presenting cells is usually about 30 amino acid residues. Therefore, in cases where the antigen-presenting cells are brought into contact with the polypeptide *in vitro*, the polypeptide may be prepared such that its length is not more than about 30 amino acid residues.

[0042] By culturing the antigen-presenting cells in the coexistence of the above-described polypeptide, the polypeptide is incorporated into MHC molecules of the antigen-presenting cells and presented on the surface of the antigen-presenting cells. Therefore, using the above-described polypeptide, isolated antigen-presenting cells containing the complex between the polypeptide and the MHC molecule can be prepared. Such antigen-presenting cells can present the polypeptide against T cells *in vivo* or *in vitro*, and induce, and allow proliferation of, cytotoxic T cells specific to the polypeptide.

[0043] By bringing the antigen-presenting cells prepared as described above having the complex between the above-described polypeptide and the MHC molecule into contact with T cells *in vitro*, cytotoxic T cells specific to the polypeptide can be induced and allowed to proliferate. This may be carried out by cocultivating the above-described antigen-presenting cells and T cells in a liquid medium. For example, it may be attained by suspending the antigen-presenting cells in a liquid medium, placing the suspension in vessels such as wells of a microplate, adding thereto T cells and then culturing the cells. The mixing ratio of the antigen-presenting cells to the T cells in the cocultivation is not restricted, and is usually about 1:1 to 1:100, preferably about 1:5 to 1:20 in terms of the number of cells. The density of the antigen-presenting cells suspended in the liquid medium is not restricted, and is usually about 100 to 10,000,000 cells/ml, preferably about 10,000 to 1,000,000 cells/ml. The cocultivation is preferably carried out at 37°C under atmosphere of 5% CO₂ in accordance with a conventional method. The culturing time is not restricted, and is usually 2 days to 3 weeks, preferably about 4 days to 2 weeks. The cocultivation is preferably carried out in the presence of one or more interleukins such as IL-2, IL-6, IL-7 and IL-12. In this case, the concentration of IL-2 and IL-7 is usually about 5 U/ml to 20 U/ml, the concentration of IL-6 is usually about 500 U/ml to 2000 U/ml, and the concentration of IL-12 is usually about 5 ng/ml to 20 ng/ml, but the concentrations of the interleukins are not restricted thereto. The above-described cocultivation may be repeated once to several times adding fresh antigen-presenting cells. For example, the operation of discarding the culture supernatant after the cocultivation and adding a fresh suspension of antigen-presenting cells to further conduct the cocultivation may be repeated once to several times. The conditions of the each cocultivation may be the same as described above.

[0044] By the above-described cocultivation, cytotoxic T cells specific to the polypeptide are induced and allowed to proliferate. Thus, using the above-described polypeptide, isolated T cells can be prepared which selectively bind the complex between the polypeptide and the MHC molecule.

[0045] As described in the Examples below, the genes encoding the polypeptides of SEQ ID NOs:2, 16, 26, 28 and 39 and SEQ ID NOs:4, 18, 30 and 41 are expressed specifically in cancer cells and testis of dogs and humans, respectively. Thus, in cancer cells, significantly higher numbers of the polypeptides of SEQ ID NOs:2, 16, 26, 28 and 39 or SEQ ID NOs:4, 18, 30 and 41 exist than in normal cells. When cytotoxic T cells prepared as described above are administered to a living body while a part of the polypeptides existing in cancer cells are presented by MHC molecules on the surfaces of the cancer cells, the cytotoxic T cells can damage the cancer cells using the presented polypeptides as markers. Since antigen-presenting cells presenting the above-described polypeptides can induce, and allow proliferation of, cytotoxic T cells specific to the polypeptides also *in vivo*, cancer cells can be damaged also by administering the antigen-presenting cells to a living body. That is, the above-described cytotoxic T cells and the above-described antigen-presenting cells prepared using the above-described polypeptide are also effective as therapeutic and/or prophylactic agents for a cancer(s).

[0046] In cases where the above-described isolated antigen-presenting cells or isolated T cells are administered to a living body, these are preferably prepared by treating antigen presenting cells or T cells collected from the patient to be treated with the polypeptide (a) to (c) as described above in order to avoid the immune response in the living body that attacks these cells as foreign bodies.

[0047] The therapeutic and/or prophylactic agent for a cancer(s) comprising as an effective ingredient the antigen-presenting cells or T cells is preferably administered via a parenteral administration route such as intravenous or intraarterial administration. The dose is appropriately selected depending on the symptom, the purpose of administration and the like, and is usually 1 cell to 10,000,000,000,000 cells, preferably 1,000,000 cells to 1,000,000,000 cells, which dose is preferably administered once per several days to once per several months. The formulation may be, for example, the cells suspended in physiological buffered saline, and the formulation may be used in combination with another/other anticancer preparation(s) and/or cytokine(s). Further, one or more additives well-known in the field of formulation of pharmaceuticals may also be added.

[0048] Also by expression of the polynucleotide encoding the above-described polypeptide (a) to (c) in the body of the animal to be treated, antibody production and cytotoxic T cells can be induced in the living body, and an effect comparable to the administration of a polypeptide can be obtained. That is, the immunity-inducing agent of the present invention may be one comprising as an effective ingredient a recombinant vector having a polynucleotide encoding the above-described polynucleotide (a) to (c), which recombinant vector is capable of expressing the polypeptide in a living body. Such a recombinant vector capable of expressing an antigenic polypeptide is also called gene vaccine. The vector used for production of a gene vaccine is not restricted as long as it is a vector capable of expressing a polypeptide in cells of the animal to be treated (preferably in a mammalian cell), and may be either a plasmid vector or a virus vector, and any known vector in the field of gene vaccines may be used. The polynucleotide such as DNA or RNA encoding the above-described polypeptide can be easily prepared, as mentioned above, by a conventional method. Incorporation of the polynucleotide into a vector can be carried out using a method well-known to those skilled in the art.

[0049] The administration route of the gene vaccine is preferably a parenteral route such as intramuscular, subcutaneous, intravenous or intraarterial administration, and the dose may be appropriately selected depending on the type of the antigen and the like, and usually about 0.1 μ g to 100 mg, preferably about 1 μ g to 10 mg in terms of the weight of the gene vaccine per 1 kg of body weight.

[0050] Methods using a virus vector include those wherein a polynucleotide encoding the above-described polypeptide is incorporated into an RNA virus or DNA virus such as retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, pox virus, poliovirus or Sindbis virus, and then the animal to be treated is infected by the resulting virus. Among these methods, those using retrovirus, adenovirus, adeno-associated virus, vaccinia virus or the like are especially preferred.

[0051] Other methods include a method wherein an expression plasmid is directly intramuscularly administered (DNA vaccine method), the liposome method, lipofectin method, microinjection method, calcium phosphate method, electroporation method and the like, and the DNA vaccine method and liposome method are especially preferred.

[0052] Methods for actually making the gene encoding the above-described polypeptide of the present invention act as a pharmaceutical include the *in vivo* method wherein the gene is directly introduced into the body, and the *ex vivo* method wherein a kind of cells are collected from the animal to be treated, the gene is introduced into the cells *ex vivo*, and then the cells are returned to the body (Nikkei Science, 1994, April, p. 20-45; The Pharmaceutical Monthly, 1994, Vol. 36, No. 1, p. 23-48; Experimental Medicine, Extra Edition, 1994, Vol. 12, No. 15; and references cited in these papers and the like). The *in vivo* method is more preferred.

[0053] In cases where the gene is administered by the *in vivo* method, the gene may be administered through an appropriate administration route depending on the disease to be treated, symptom and so on. It may be administered, for example, by intravenous, intraarterial, subcutaneous, intramuscular administration or the like. In cases where the gene is administered by the *in vivo* method, the gene may be formulated into a preparation such as a solution, and in general, it is formulated into an injection solution or the like containing the DNA encoding the above-described peptide of the present invention as an effective ingredient. A commonly used carrier(s) may be added as required. In the case of a liposome or membrane fusion liposome (Sendai virus (HVJ)-liposome or the like) containing the DNA, the liposome may be formulated into a liposome preparation such as a suspension, frozen preparation or centrifugally concentrated frozen preparation.

[0054] In the present invention, "the base sequence shown in SEQ ID NO:1" includes not only the base sequence expressly written in SEQ ID NO:1, but also the sequence complementary thereto. Thus, "a polynucleotide having the base sequence shown in SEQ ID NO:1" includes a single-stranded polynucleotide having the base sequence expressly written in SEQ ID NO:1, a single-stranded polynucleotide having the base sequence complementary thereto, and a double-stranded polynucleotide composed of these single strand polynucleotides. When the polynucleotide encoding the polypeptide used in the present invention is prepared, any one of these base sequences should be appropriately selected, and those skilled in the art can easily carry out the selection.

EXAMPLES

[0055] The present invention will now be described more concretely by way of Examples.

Example A-1: Acquisition of Novel Cancer Antigen Protein by SEREX Method

(1) Preparation of cDNA Library

[0056] Total RNA was prepared from testis tissue of a healthy dog by the Acid guanidium-Phenol-Chloroform method, and poly(A) RNA was purified using Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) in accordance with the protocol attached to the kit.

[0057] Using the obtained mRNA (5 μ g), a dog testis cDNA phage library was synthesized. Preparation of the cDNA phage library was carried out using cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA Gigapack III Gold Cloning Kit (manufactured by STRATAGENE) in accordance with the protocols attached to the kits. The size of the prepared cDNA phage library was 1.3×10^6 pfu/ml.

(2) Screening of cDNA Library with Serum

[0058] Using the dog testis-derived cDNA phage library prepared as described above, immunoscreening was carried out. More particularly, host *E. coli* cells (XL1-Blue MRF') were infected with the library such that 2,340 clones should appear on an NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and cultured at 42°C for 3 to 4 hours to allow the phage to form plaques. The plate was covered with nitrocellulose membrane (Hybond C Extra: manufactured by GE Healthcare Bio-Science) impregnated with IPTG (isopropyl- β -D-thiogalactoside) at 37°C for 4 hours to induce and express proteins, which were thus transferred to the membrane. Subsequently, the membrane was recovered and soaked in TBS (10 mM Tris-HCl, 150 mM NaCl; pH 7.5) containing 0.5% non-fat dry milk, followed by shaking it at 4°C overnight to suppress non-specific reactions. This filter was allowed to react with 500-fold diluted canine patient serum at room temperature for 2 to 3 hours.

[0059] As the above-described canine patient serum, serum collected from canine patients suffering from squamous cell carcinoma was used. The serum was stored at -80°C and pretreated immediately before use. The method of the pretreatment of the serum was as follows. That is, host *E. coli* cells (XL1-Blue MRF') were infected with λ ZAP Express phage to which no foreign gene was inserted, and then cultured on NZY plate medium at 37°C overnight. Subsequently, the buffer of 0.2 M NaHCO₃, pH 8.3 containing 0.5 M NaCl was added to the plate, and the plate was left to stand at 4°C for 15 hours, followed by collecting the supernatant as an *E. coli*/phage extract. Thereafter, the collected *E. coli*/phage extract was allowed to flow through an NHS column (manufactured by GE Healthcare Bio-Science) to immobilize proteins derived from the *E. coli*/phage thereon. The serum from the canine patients was allowed to flow through and react with this protein-immobilized column to remove antibodies adsorbed on *E. coli* and/or the phage. The serum fraction that passed through the column was 500-fold diluted with TBS containing 0.5% non-fat dry milk, and the resulting diluent was used as the material for the immunoscreening.

[0060] The membrane on which the thus treated serum and the above-described fusion protein were blotted was washed 4 times with TBS-T (0.05% Tween 20/TBS), and allowed to react with goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated: manufactured by BETHYL Laboratories) 5000-fold diluted with TBS containing 0.5% non-fat dry milk as a secondary antibody at room temperature for 1 hour, followed by detection by the enzyme coloring reaction using the NBT/BCIP reaction solution (manufactured by Roche). Colonies at positions where a positive coloring reaction was observed were recovered from the NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and dissolved in 500 μ l of SM buffer (100 mM NaCl, 10 mM MgClSO₄, 50 mM Tris-HCl, 0.01% gelatin; pH 7.5). The screening was repeated as a second and third screening in the same manner as described above until a single coloring reaction-positive colony was obtained, thereby isolating one positive clone after screening of 30,940 phage clones reactive with IgG in the serum.

(3) Homology Search of Isolated Antigen Gene

[0061] To subject the single positive clone isolated by the above-described method to a base sequence analysis, an operation of conversion of the phage vector to a plasmid vector was carried out. More particularly, 200 μ l of a solution prepared to contain a host *E. coli* (XL1-Blue MRF') such that the absorbance OD₆₀₀ should be 1.0 was mixed with 100 μ l of a purified phage solution and further with 1 μ l of ExAssist helper phage (manufactured by STRATAGENE), and the reaction was allowed to proceed at 37°C for 15 minutes. To the reaction mixture, 3 ml of LB medium was added, and the mixture was cultured at 37°C for 2.5 to 3 hours, followed by immediate incubation in a water bath at 70°C for 20 minutes. The mixture was then centrifuged at 4°C at 1000 $\times$ g for 15 minutes, and the supernatant was recovered as a phagemid solution. Subsequently, 200 μ l of a solution prepared to contain a phagemid host *E. coli* (SOLR) such that the absorbance OD₆₀₀ should be 1.0 was mixed with 10 μ l of a purified phage solution, and the reaction was allowed to proceed at 37°C for 15 minutes. Thereafter, 50 μ l of the reaction mixture was plated on ampicillin (final concentration: 50 μ g/ml)-containing LB agar medium, and cultured at 37°C overnight. A single colony of transformed SOLR was recovered and cultured in ampicillin (final concentration: 50 μ g/ml)-containing LB medium at 37°C, followed by purification

of plasmid DNA having an insert of interest using QIAGEN plasmid Miniprep Kit (manufactured by Qiagen).

[0062] The purified plasmid was subjected to an analysis of the entire sequence of the insert by the primer walking method using the T3 primer described in SEQ ID NO:5 and the T7 primer described in SEQ ID NO:6. By this sequence analysis, the gene sequence described in SEQ ID NO:1 was obtained. Using the base sequence and the amino acid sequence of this gene, homology search against known genes was carried out using a homology search program BLAST (<http://www.ncbi.nlm.nih.gov/BLAST/>). As a result, it was revealed that the obtained gene is the gene (Accession No. XM_535343) encoding a protein (Accession No. XP_535343) whose function is unknown. The human homologous factor of this gene was the gene (Accession No. NM_152660) encoding a protein (Accession No. NP_689873) whose function is also unknown (homology: base sequence, 93%; amino acid sequence, 99%). The base sequence of the human homologous factor is shown in SEQ ID NO:3, and the amino acid sequence thereof is shown in SEQ ID NO:4.

(4) Analysis of Expression in Each Tissue

[0063] The expression of the gene, which was obtained by the above-described method, in normal tissues and various cell lines of dog and human were investigated by the RT-PCR (Reverse Transcription-PCR) method. The reverse transcription reaction was carried out as follows. That is, total RNA was extracted from 50 to 100 mg of each tissue or 5 to 10×10^6 cells of each cell line using TRIzol reagent (manufactured by Invitrogen) in accordance with the protocol attached to the kit. Using this total RNA, cDNA was synthesized by Superscript First-Strand Synthesis System for RT-PCR (manufactured by Invitrogen) in accordance with the protocol attached to the kit. As the cDNAs from human normal tissues (brain, hippocampus, testis, colon and placenta), Gene Pool cDNA (manufactured by Invitrogen), QUICK-Clone cDNA (manufactured by CLONTECH) and Large-Insert cDNA Library (manufactured by CLONTECH) were used. The PCR reactions were carried out as follows using primers (described in SEQ ID NOs:7 and 8) specific to the obtained canine gene and its human homologous gene. That is, respective reagents and the attached buffer were mixed such that the mixture should contain $0.25 \mu\text{l}$ of the sample prepared by the reverse transcription reaction, $2 \mu\text{M}$ each of the above primers, 0.2 mM each of dNTP and 0.65 U of ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of $25 \mu\text{l}$, and the reaction was carried out with 30 cycles of 94°C for 30 seconds, 55°C for 30 seconds and 72°C for 1 minute using Thermal Cycler (manufactured by BIO RAD). The gene-specific primers having the base sequences shown in the above-described SEQ ID NOs:7 and 8 were those which amplify the regions of the 87th to 606th bases of the base sequence of SEQ ID NO:1 and the 173rd to 695th bases of the base sequence of SEQ ID NO:3, and can be used for investigation of the expression of both the canine gene and its human homologous gene. As a control for comparison, primers (described in SEQ ID NOs:9 and 10) specific to GAPDH were used simultaneously. As a result, as shown in Fig. 1, strong expression of the obtained canine gene was observed in testis among the normal dog tissues, and on the other hand, strong expression was observed in the canine breast cancer cell line. Expression of the human homologous gene was confirmed, as is the case with the canine gene, only in testis among the human normal tissues, but the expression was detected in brain tumor, leukemia, breast cancer and lung cancer cells among human cancer cell lines. Thus, the human homologous gene was also confirmed to be specifically expressed in testis and cancer cells.

[0064] In Fig. 1, reference numeral 1 in the ordinate indicates the expression pattern of the above identified gene, and reference numeral 2 indicates the expression pattern of the *GAPDH* gene as a control for comparison.

Example A-2: Preparation of Novel Cancer Antigen Proteins

(1) Preparation of Recombinant Protein

[0065] Based on the gene of SEQ ID NO:1 obtained in Example A-1, a recombinant protein was prepared by the following method. Respective reagents and the attached buffer were mixed such that the mixture should contain $1 \mu\text{l}$ of the vector which was prepared from the phagemid solution obtained in Example A-1 and was subjected to the sequence analysis, $0.4 \mu\text{M}$ each of two kinds of primers having *NdeI* and *XhoI* restriction sites (described in SEQ ID NOs:11 and 12), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of $50 \mu\text{l}$, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 1 minute using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:2. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 930 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0066] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *NdeI* and *XhoI* and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET16b (manufactured by Novagen)

that had been treated with *Nde*I and *Xho*I. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

[0067] On the other hand, based on the gene of SEQ ID NO:3, a recombinant protein of the human homologous gene was prepared by the following method. Respective reagents and the attached buffer were mixed such that the mixture should contain 1 μ l of the cDNA prepared in Example A-1 whose expression could be confirmed by the RT-PCR method in various tissues/cells, 0.4 μ M each of two kinds of primers having *Eco*RV and *Eco*RI restriction sites (described in SEQ ID NOs:13 and 14), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 50 μ l, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 1 minute using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:4. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 930 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0068] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *Eco*RV and *Eco*RI and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with *Eco*RV and *Eco*RI. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

(2) Purification of Recombinant Protein

[0069] The above-obtained recombinant *E. coli* cells that expressed SEQ ID NO:1 and SEQ ID NO:3, respectively, were cultured in 100 μ g/ml ampicillin-containing LB medium at 37°C until the absorbance at 600 nm reached about 0.7, and then isopropyl- β -D-1-thiogalactopyranoside was added thereto such that its final concentration should be 1 mM, followed by culturing them at 37°C for 4 hours. Subsequently, the cells were collected by centrifugation at 4,800 rpm for 10 minutes. The pellet of the cells was suspended in phosphate-buffered saline and further subjected to centrifugation at 4,800 rpm for 10 minutes to wash the cells.

[0070] The cells were suspended in 50 mM Tris-HCl buffer (pH 8.0) and subjected to sonication on ice. The sonicated solution of *E. coli* was centrifuged at 6,000 rpm for 20 minutes to obtain the supernatant as the soluble fraction and the precipitate as the insoluble fraction.

[0071] The insoluble fraction was suspended in 50 mM Tris-HCl buffer (pH 8.0) and centrifuged at 6,000 rpm for 15 minutes. This operation was repeated twice and an operation of removal of proteases was carried out.

[0072] The residue was suspended in 6M guanidine hydrochloride, 0.15 M sodium chloride-containing 50 mM Tris-HCl buffer (pH 8.0), and the resulting suspension was left to stand at 4°C for 20 hours to denature proteins. Thereafter, the suspension was centrifuged at 6,000 rpm for 30 minutes, and the obtained soluble fraction was placed in a nickel chelate column prepared by a conventional method (carrier: Chelating Sepharose (trademark) Fast Flow (GE Health Care); column volume: 5mL; equilibration buffer: 6M guanidine hydrochloride, 0.15 M sodium chloride-containing 50 mM Tris-HCl buffer (pH 8.0)), followed by leaving it to stand at 4°C overnight to allow adsorption to the nickel-chelated carrier. The supernatant was recovered by centrifugation of this column carrier at 1,500 rpm for 5 minutes, and the column carrier was suspended in phosphate-buffered saline, followed by refilling the column with the resulting suspension.

[0073] The fraction that was not adsorbed to the column was washed away with 10 column volumes of 0.5 M sodium chloride-containing 0.1 M acetate buffer (pH 4.0), and elution was immediately carried out with 0.5 M sodium chloride-containing 0.1 M acetate buffer (pH 3.0) to obtain a purified fraction, which was used as the material for administration tests thereafter. The proteins of interest in respective eluted fractions were confirmed by Coomassie staining carried out according to a conventional method. Among these, the canine protein of interest is shown in Fig. 2.

[0074] The buffer contained in the purified preparation obtained by the above-described method was replaced with a reaction buffer (50mM Tris-HCl, 100mM NaCl, 5mM CaCl_2 ; pH8.0), and cleavage of His tag by Factor Xa protease and purification of the protein of interest were carried out, using FactorXa Cleavage Capture Kit (manufactured by Novagen), in accordance with the protocols attached to the kit. Subsequently, the buffer contained in 1.2 ml of the purified preparation obtained by the above-described method was replaced with physiological phosphate buffer (manufactured by Nissui Pharmaceutical) by ultrafiltration using NANOSEP 10K OMEGA (manufactured by PALL), and the resulting solution was filtered aseptically using HT Tuffryn Acrodisc 0.22 μ m (manufactured by PALL) and used in the following experiments.

Example A-3: Test of Administration of Recombinant Protein to Cancer-bearing Dogs

(1) Antitumor Assay

[0075] The anti-tumor effect of the two kinds of recombinant proteins which were purified as described above was assessed in two individuals of cancer-bearing dogs having epidermal tumor (2 individuals having mammary gland tumor).

[0076] An equal amount of Freund's incomplete adjuvant (manufactured by Wako Pure Chemicals) was mixed with 100 μg (0.5 ml) of the recombinant polypeptides (derived from dog and human), respectively, to prepare two kinds of therapeutic agents for a cancer(s). Each of these agents was administered to a regional lymph node in the vicinity of the tumor a total of 3 times, by carrying out the subsequent administrations 3 days and 7 days after the first administration. As a result, the tumors with a size of about 25 mm^3 and 50 mm^3 at the time of administration of the therapeutic agents for a cancer(s) (derived from dog and human), respectively, were reduced in size to 20 mm^3 and 42 mm^3 , respectively, 10 days after the first administration; 13 mm^3 and 26 mm^3 , respectively, 20 days after the first administration; and to 5 mm^3 and 10 mm^3 , respectively, 30 days after the first administration.

[0077] Further, to a canine patient suffering from malignant melanoma, a mixture of 100 μg (0.5 ml) of the above-described polypeptide derived from dog and 0.5 ml of Freund's incomplete adjuvant was administered intracutaneously at the periphery of the tumor a total of 3 times at the same intervals as described above. Further, concurrently with the respective administrations, 10 MU of "Intercat" which is a recombinant feline interferon was administered subcutaneously. As a result, the tumor with a size of about 142 mm^3 at the time of administration of the therapeutic agent for a cancer(s) completely regressed 29 days after the first administration.

[0078] Further, to a canine patient suffering from nasal adenocarcinoma, a mixture of 100 μg (0.5 ml) of the above-described polypeptide derived from dog and 0.5 ml of Freund's incomplete adjuvant was administered in the same manner as described above a total of 3 times. Further, concurrently with the respective administrations, 100 μg of canine interleukin 12 was administered subcutaneously. As a result, the tumor with a size of about 57 mm^3 at the time of administration of the therapeutic agent for a cancer(s) completely regressed 14 days after the first administration.

(2) Immune Inducibility Assay

[0079] Blood from the canine patient in which the anti-tumor effect was obtained in the administration test in the above-described (1) was collected before administration of the therapeutic agent for a cancer(s), and 10 days and 30 days after the first administration. Peripheral blood mononuclear cells were isolated according to a conventional method, and by the ELISPOT assay for $\text{IFN}\gamma$ using it, the immune inducibility of each administered recombinant protein was assayed.

[0080] In a 96-well plate manufactured by Millipore (MultiScreen-IP, MAIPS 4510), 100 μL /well of 70% ethanol was placed and the plate was left to stand for 5 minutes, followed by removal of the ethanol by aspiration. The plate was washed with sterile water and 300 μL /well of 200 mM Sodium Bicarbonate (pH8.2) was placed therein. After leaving it to stand for 5 minutes, Sodium Bicarbonate was removed by aspiration, and then the plate was washed. Subsequently, 0.5 μL /well of anti-canine interferon γ monoclonal antibody (manufactured by R&D, clone 142529, MAB781) mixed with 200 mM Sodium Bicarbonate was placed in wells, and the plate was incubated at 37°C overnight to immobilize the primary antibody. After removal of the primary antibody by aspiration, 300 μL /well of a blocking solution (1% BSA-5% sucrose-200 mM Sodium Bicarbonate (pH8.2)) was added to the wells, and the plate was incubated at 4°C overnight to block the plate. After removal of the blocking solution by aspiration, 300 μL /well of 10% fetal calf serum-containing RPMI medium (manufactured by Invitrogen) was placed in the wells, and the plate was left to stand for 5 minutes, followed by removal of the medium by aspiration. Subsequently, 5×10^5 cells/well of the canine peripheral blood mononuclear cells suspended in 10% fetal calf serum-containing RPMI medium were placed in the plate, and 10 μL /well of the canine-derived polypeptide or human-derived polypeptide used in each administration was added thereto, followed by culturing the cells under the conditions of 37°C and 5% CO_2 for 24 hours, to allow immunocytes that might exist in the peripheral blood mononuclear cells to produce interferon γ . After the culture, the medium was removed, and the wells were washed 6 times with a washing solution (0.1% Tween20-200mM Sodium Bicarbonate (pH8.2)). In each well, 100 μL of rabbit anti-dog polyclonal antibody 1000-fold diluted with the above-described blocking solution was placed, and the plate was incubated at 4°C overnight. After washing the wells 3 times with the above-described washing solution, 100 μL of HRP-labeled anti-rabbit antibody 1000-fold diluted with the above-described blocking solution was placed in each well, and the reaction was allowed to proceed at 37°C for 2 hours. After washing the wells 3 times with the above-described washing solution, the resultant was colored with Konica Immunostain (manufactured by Konica), and the wells were washed with water to stop the reaction. Thereafter, the membrane was dried, and the number of the appeared spots was counted using KS ELISPOT (manufactured by Carl Zeiss, Inc.).

[0081] As a result, in either canine patient to which the canine polypeptide or the human polypeptide was administered, peripheral blood mononuclear cells sampled before the administration of the polypeptide showed no spots. On the other hand, in the canine patient to which the canine polypeptide was administered, peripheral blood mononuclear cells

sampled 10 days and 30 days after the administration showed 20 and 36 spots, respectively. In the canine patient to which the human polypeptide was administered, peripheral blood mononuclear cells sampled 10 days and 30 days after the administration showed 24 and 36 spots, respectively.

[0082] From the above results, it is confirmed that immunocytes which specifically react with the administered recombinant protein and produce interferon γ were induced in all of the canine patients to which the recombinant protein was administered, and it is thought that the anti-tumor effect described in (1) was exerted by immunoreactions in which these immunocytes are mainly involved.

Example B-1: Acquisition of Novel Cancer Antigen Protein by SEREX Method

(1) Preparation of cDNA Library

[0083] Total RNA was prepared from testis tissue of a healthy dog by the Acid guanidium-Phenol-Chloroform method, and poly(A) RNA was purified using Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) in accordance with the protocol attached to the kit.

[0084] Using the obtained mRNA (5 μ g), a dog testis cDNA phage library was synthesized. Preparation of the cDNA phage library was carried out using cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA Gigapack III Gold Cloning Kit (manufactured by STRATAGENE) in accordance with the protocols attached to the kits. The size of the prepared cDNA phage library was 1.3×10^6 pfu/ml.

(2) Screening of cDNA Library with Serum

[0085] Using the dog testis-derived cDNA phage library prepared as described above, immunoscreening was carried out. More particularly, host *E. coli* cells (XL1-Blue MRF') were infected with the library such that 2,340 clones should appear on an NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and cultured at 42°C for 3 to 4 hours to allow the phage to form plaques. The plate was covered with nitrocellulose membrane (Hybond C Extra: manufactured by GE Healthcare Bio-Science) impregnated with IPTG (isopropyl- β -D-thiogalactoside) at 37°C for 4 hours to induce and express proteins, which were thus transferred to the membrane. Subsequently, the membrane was recovered and soaked in TBS (10 mM Tris-HCl, 150 mM NaCl; pH 7.5) containing 0.5% non-fat dry milk, followed by shaking at 4°C overnight to suppress non-specific reactions. This filter was allowed to react with 500-fold diluted canine patient serum at room temperature for 2 to 3 hours.

[0086] As the above-described canine patient serum, serum collected from canine patients suffering from tumor proximal to the anus was used. The serum was stored at -80°C and pretreated immediately before use. The method of the pretreatment of the serum was as follows. That is, host *E. coli* cells (XL1-Blue MRF') were infected with λ ZAP Express phage to which no foreign gene was inserted, and then cultured on NZY plate medium at 37°C overnight. Subsequently, the buffer of 0.2 M NaHCO₃, pH 8.3 containing 0.5 M NaCl was added to the plate, and the plate was left to stand at 4°C for 15 hours, followed by collecting the supernatant as an *E. coli*/phage extract. Thereafter, the collected *E. coli*/phage extract was allowed to flow through an NHS column (manufactured by GE Healthcare Bio-Science) to immobilize proteins derived from the *E. coli*/phage thereon. The serum from the canine patients was allowed to flow through and react with this protein-immobilized column to remove antibodies adsorbed on *E. coli* and/or the phage. The serum fraction that passed through the column was 500-fold diluted with TBS containing 0.5% non-fat dry milk, and the resulting diluent was used as the material for the immunoscreening.

[0087] The membrane on which the thus treated serum and the above-described fusion protein were blotted was washed 4 times with TBS-T (0.05% Tween 20/TBS), and allowed to react with goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated: manufactured by BETHYL Laboratories) 5000-fold diluted with TBS containing 0.5% non-fat dry milk as a secondary antibody at room temperature for 1 hour, followed by detection by the enzyme coloring reaction using the NBT/BCIP reaction solution (manufactured by Roche). Colonies at positions where a positive coloring reaction was observed were recovered from the NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and dissolved in 500 μ l of SM buffer (100 mM NaCl, 10 mM MgClSO₄, 50 mM Tris-HCl, 0.01% gelatin; pH 7.5). The screening was repeated as a second and third screening in the same manner as described above until a single coloring reaction-positive colony was obtained, thereby isolating one positive clone after screening of 30,940 phage clones reactive with IgG in the serum.

(3) Homology Search of Isolated Antigen Gene

[0088] To subject the single positive clone isolated by the above-described method to a base sequence analysis, an operation of conversion of the phage vector to a plasmid vector was carried out. More particularly, 200 μ l of a solution prepared to contain a host *E. coli* (XL1-Blue MRF') such that the absorbance OD₆₀₀ should be 1.0 was mixed with 100 μ l of a purified phage solution and further with 1 μ l of ExAssist helper phage (manufactured by STRATAGENE), and

the reaction was allowed to proceed at 37°C for 15 minutes. To the reaction mixture, 3 ml of LB medium was added, and the mixture was cultured at 37°C for 2.5 to 3 hours, followed by immediate incubation in a water bath at 70°C for 20 minutes. The mixture was then centrifuged at 4°C at 1000 xg for 15 minutes, and the supernatant was recovered as a phagemid solution. Subsequently, 200 μ l of a solution prepared to contain a phagemid host *E. coli* (SOLR) such that the absorbance OD₆₀₀ should be 1.0 was mixed with 10 μ l of a purified phage solution, and the reaction was allowed to proceed at 37°C for 15 minutes. Thereafter, 50 μ l of the reaction mixture was plated on ampicillin (final concentration: 50 μ g/ml)-containing LB agar medium, and cultured at 37°C overnight. A single colony of transformed SOLR was recovered and cultured in ampicillin (final concentration: 50 μ g/ml)-containing LB medium at 37°C, followed by purification of plasmid DNA having an insert of interest using QIAGEN plasmid Miniprep Kit (manufactured by Qiagen).

[0089] The purified plasmid was subjected to an analysis of the entire sequence of the insert by the primer walking method using the T3 primer described in SEQ ID NO:5 and the T7 primer described in SEQ ID NO:6. By this sequence analysis, the gene sequence described in SEQ ID NO:15 was obtained. Using the base sequence and the amino acid sequence of this gene, homology search against known genes was carried out using a homology search program BLAST (<http://www.ncbi.nlm.nih.gov/BLAST/>). As a result, it was revealed that the obtained gene is the calmegin gene. The human homologous factor of the canine calmegin gene was human calmegin (homology: base sequence, 90%; amino acid sequence, 89%). The base sequence of human calmegin is shown in SEQ ID NO:17, and the amino acid sequence thereof is shown in SEQ ID NO:18.

(4) Analysis of Expression in Each Tissue

[0090] The expression of the gene, which was obtained by the above-described method, in normal tissues and various cell lines of dog and human were investigated by the RT-PCR (Reverse Transcription-PCR) method. The reverse transcription reaction was carried out as follows. That is, total RNA was extracted from 50 to 100 mg of each tissue or 5 to 10 $\times 10^6$ cells of each cell line using TRIZOL reagent (manufactured by Invitrogen) in accordance with the protocol attached to the kit. Using this total RNA, cDNA was synthesized by Superscript First-Strand Synthesis System for RT-PCR (manufactured by Invitrogen) in accordance with the protocol attached to the kit. As the cDNAs from human normal tissues (brain, hippocampus, testis, colon and placenta), Gene Pool cDNA (manufactured by Invitrogen), QUICK-Clone cDNA (manufactured by CLONTECH) and Large-Insert cDNA Library (manufactured by CLONTECH) were used. The PCR reactions were carried out as follows using primers (described in SEQ ID NOs:19 and 20) specific to the obtained gene. That is, respective reagents and the attached buffer were mixed such that the mixture should contain 0.25 μ l of the sample prepared by the reverse transcription reaction, 2 μ M each of the above primers, 0.2 mM each of dNTP and 0.65 U of ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 25 μ l, and the reaction was carried out with 30 cycles of 94°C for 30 seconds, 55°C for 30 seconds and 72°C for 1 minute using Thermal Cycler (manufactured by BIO RAD). The above-described gene-specific primers were those which amplify the regions of the 755th to 1318th bases of the base sequence of SEQ ID NO:15 (canine calmegin gene) and the 795th to 1358th bases of the base sequence of SEQ ID NO:17 (human calmegin gene), and can be used for investigation of the expression of both the canine calmegin gene and the human calmegin gene. As a control for comparison, primers (described in SEQ ID NOs:9 and 10) specific to GAPDH were used simultaneously. As a result, as shown in Fig. 3, strong expression of the canine calmegin gene was observed in testis among the normal dog tissues, and on the other hand, strong expression was observed in canine tumor cell lines. Expression of the human calmegin gene was confirmed, as is the case with the canine calmegin gene, only in testis among the human normal tissues, but the expression was detected in brain tumor, leukemia and esophagus cancer cells among human cancer cell lines. Thus, the human calmegin gene was also confirmed to be specifically expressed in testis and cancer cells.

[0091] In Fig. 3, reference numeral 1 in the ordinate indicates the expression pattern of the calmegin gene, and reference numeral 2 indicates the expression pattern of the *GAPDH* gene as a control for comparison.

Example B-2: Preparation of Canine and Human Calmegin Proteins

(1) Preparation of Recombinant Protein

[0092] Based on the gene of SEQ ID NO:15 obtained in Example B-1, a recombinant protein was prepared by the following method. Respective reagents and the attached buffer were mixed such that the mixture should contain 1 μ l of the vector that was prepared from the phagemid solution obtained in Example B-1 and was subjected to the sequence analysis, 0.4 μ M each of two kinds of primers having *Bam*HI and *Eco*RI restriction sites (described in SEQ ID NOs:21 and 22), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 50 μ l, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 2 minutes using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:16. After the PCR, the amplified DNA was

subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 1.9 kbp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0093] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *Bam*HI and *Eco*RI and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with *Bam*HI and *Eco*RI. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

[0094] On the other hand, based on the gene of SEQ ID NO:17, a recombinant protein of the human homologous gene was prepared by the following method. Respective reagents and the attached buffer were mixed such that the mixture should contain 1 μ l of the cDNA prepared in Example B-1 whose expression could be confirmed by the RT-PCR method in various tissues/cells, 0.4 μ M each of two kinds of primers having *Eco*RI and *Xho*I restriction sites (described in SEQ ID NOs:23 and 24), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 50 μ l, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 2 minutes using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:18. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 1.9 kbp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0095] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *Eco*RI and *Xho*I and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with *Eco*RI and *Xho*I. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

(2) Purification of Recombinant Protein

[0096] The above-obtained recombinant *E. coli* cells that expressed SEQ ID NO:15 and SEQ ID NO:17, respectively, were cultured in 30 μ g/ml kanamycin-containing LB medium at 37°C until the absorbance at 600 nm reached about 0.7, and then isopropyl- β -D-1-thiogalactopyranoside was added thereto such that its final concentration should be 1 mM, followed by culturing them at 37°C for 4 hours. Subsequently, the cells were collected by centrifugation at 4,800 rpm for 10 minutes. The pellet of the cells was suspended in phosphate-buffered saline and further subjected to centrifugation at 4,800 rpm for 10 minutes to wash the cells.

[0097] The obtained pellet of *E. coli* cells was suspended in 20 mM phosphate buffer (pH 7.0) and subjected to sonication on ice. The sonicated solution of *E. coli* was centrifuged at 6,000 rpm for 20 minutes to obtain the supernatant as the soluble fraction and the precipitate as the insoluble fraction.

[0098] The soluble fraction was placed in an ion-exchange column (carrier: SP Sepharose (trademark) Fast Flow (GE Health Care); column volume: 5mL; equilibration buffer: 20 mM phosphate buffer (pH 7.0)). The column was washed with 10 column volumes of 20 mM phosphate buffer (pH 7.0), and elution was carried out with density gradient of salt by 0.3 M-1.0 M sodium chloride-containing 20 mM phosphate buffer (pH 7.0). Six column volumes of the eluted fraction was collected in each elution step.

[0099] Among these eluted fractions, the 1st to 6th fractions eluted with 0.3 M sodium chloride-containing 20 mM phosphate buffer (pH 7.0) and the 1st fraction eluted with 1.0 M sodium chloride-containing 20 mM phosphate buffer (pH 7.0) were combined, and the resulting solution was subjected to additional purification by a secondary column.

[0100] For the secondary column, a column carrier Bio gel HT Type II (BioRad) was used. The column volume was 5 mL. The column was equilibrated with 10 column volumes of 0.3 M sodium chloride-containing 20 mM phosphate buffer (pH 7.0), and the above-described eluted fractions were placed in the column. The fractions that were not adsorbed to the column was washed away with 10 column volumes of 0.3 M sodium chloride-containing 20 mM phosphate buffer (pH 7.0) and 0.1 M phosphate buffer (pH 7.0), and elution was carried out with 0.2 M phosphate buffer (pH 7.0) to obtain a purified fraction, which was used as the material for administration tests thereafter. The proteins of interest in the eluted fractions were confirmed by Coomassie staining carried out according to a conventional method. Among these, the canine calmodulin protein is shown in Fig. 4.

[0101] To 1 ml of a reaction buffer (20 mM Tris-HCl, 50 mM NaCl, 2 mM CaCl_2 ; pH 7.4), 200 μ l of the purified preparation obtained by the above-described method was aliquoted, and 2 μ l of enterokinase (manufactured by Novagen)

was then added thereto, followed by leaving it to stand at room temperature overnight to cleave His tag. The resulting product was purified using Enterokinase Cleavage Capture Kit (manufactured by Novagen) in accordance with the protocol attached to the kit. Subsequently, the buffer contained in 1.2 ml of the purified preparation obtained by the above-described method was replaced with physiological phosphate buffer (manufactured by Nissui Pharmaceutical) by ultrafiltration using NANOSEP 10K OMEGA (manufactured by PALL), and the resulting solution was filtered aseptically using HT Tuffryn Acrodisc 0.22 μm (manufactured by PALL) and used in the following experiments.

Example B-3: Test of Administration of Recombinant Protein to Cancer-bearing Dogs

(1) Antitumor Assay

[0102] The anti-tumor effect of the two kinds of recombinant proteins which were purified as described above was assessed in two individuals of cancer-bearing dogs having epidermal tumor (2 individuals having mammary gland tumor).

[0103] An equal amount of Freund's incomplete adjuvant (manufactured by Wako Pure Chemicals) was mixed with 100 μg (0.5 ml) of the recombinant canine calmegin and human calmegin proteins, respectively, to prepare therapeutic agents for a cancer(s). Each of these agents was administered to a regional lymph node in the vicinity of the tumor a total of 3 times, by carrying out the subsequent administrations 3 days and 7 days after the first administration. As a result, the tumors with a size of about 45 mm^3 and 78 mm^3 , respectively, at the time of administration of the therapeutic agents were reduced to 27 mm^3 and 46 mm^3 , respectively, 10 days after the first administration; 15 mm^3 and 26 mm^3 , respectively, 20 days after the first administration; and to 7 mm^3 and 15 mm^3 , respectively, 30 days after the first administration.

[0104] Further, to a canine patient suffering from malignant melanoma, a mixture of 100 μg (0.5 ml) of the above-described canine calmegin protein and 0.5 ml of Freund's incomplete adjuvant was administered a total of 3 times in the same manner as described above. Further, concurrently with the respective administrations, 100 μg of canine interleukin 12 was administered subcutaneously. As a result, the tumor with a size of about 38 mm^3 at the time of administration of the therapeutic agent completely regressed 21 days after the first administration of the therapeutic agent.

(2) Immune Inducibility Assay

[0105] Blood from the canine patient in which the anti-tumor effect was obtained in the administration test in the above-described (1) was collected before administration of the therapeutic agent for a cancer(s) and 10 days and 30 days after the first administration. Peripheral blood mononuclear cells were isolated according to a conventional method, and by the ELISPOT assay for $\text{IFN}\gamma$ using it, the immune inducibility of each administered recombinant protein was assayed.

[0106] In a 96-well plate manufactured by Millipore (MultiScreen-IP, MAIPS 4510), 100 μL /well of 70% ethanol was placed and the plate was left to stand for 5 minutes, followed by removal of the ethanol by aspiration. The plate was washed with sterile water and 300 μL /well of 200 mM Sodium Bicarbonate (pH8.2) was placed therein. After leaving it to stand for 5 minutes, Sodium Bicarbonate was removed by aspiration, and then the plate was washed. Subsequently, 0.5 μg /well of anti-canine interferon γ monoclonal antibody (manufactured by R&D, clone 142529, MAB781) mixed with 200 mM Sodium Bicarbonate was placed in wells, and the plate was incubated at 37°C overnight to immobilize the primary antibody. After removal of the primary antibody by aspiration, 300 μL /well of a blocking solution (1% BSA-5% sucrose-200 mM Sodium Bicarbonate (pH8.2)) was added to the wells, and the plate was incubated at 4°C overnight to block the plate. After removal of the blocking solution by aspiration, 300 μL /well of 10% fetal calf serum-containing RPMI medium (manufactured by Invitrogen) was placed in the wells, and the plate was left to stand for 5 minutes, followed by removal of the medium by aspiration. Subsequently, 5×10^5 cells/well of the canine peripheral blood mononuclear cells suspended in 10% fetal calf serum-containing RPMI medium were placed in the plate, and 10 μL /well of the canine calmegin or human calmegin protein used in each administration was added thereto, followed by culturing the cells under the conditions of 37°C and 5% CO_2 for 24 hours, to allow immunocytes that might exist in the peripheral blood mononuclear cells to produce interferon γ . After the culture, the medium was removed, and the wells were washed 6 times with a washing solution (0.1% Tween20-200mM Sodium Bicarbonate (pH8.2)). In each well, 100 μL of rabbit anti-dog polyclonal antibody 1000-fold diluted with the above-described blocking solution was placed, and the resulting mixture was incubated at 4°C overnight. After washing the wells 3 times with the above-described washing solution, 100 μL of HRP-labeled anti-rabbit antibody 1000-fold diluted with the above-described blocking solution was placed in each well, and the reaction was allowed to proceed at 37°C for 2 hours. After washing the wells 3 times with the above-described washing solution, the resultant was colored with Konica Immunostain (manufactured by Konica), and the wells were washed with water to stop the reaction. Thereafter, the membrane was dried, and image processing of the wells was carried out, followed by counting the number of spot-forming cells (SFC) using KS ELISPOT compact system (Carl Zeiss, Inc., Germany).

[0107] As a result, in either canine patient to which canine calmegin or human calmegin was administered, peripheral

blood mononuclear cells sampled before the administration showed no spots. On the other hand, in the canine patient to which canine calmeglin was administered, peripheral blood mononuclear cells sampled 10 days and 30 days after the administration showed 15 and 45 spots, respectively. In the canine patient to which human calmeglin was administered, peripheral blood mononuclear cells sampled 10 days and 30 days after the administration showed 12 and 39 spots, respectively.

[0108] From the above results, it is confirmed that immunocytes which specifically react with the administered recombinant protein and produce interferon γ were induced in all of the canine patients to which the recombinant protein was administered, and it is thought that the anti-tumor effect described in (1) was exerted by immunoreactions in which these immunocytes are mainly involved.

Example C-1: Acquisition of Novel Cancer Antigen Protein by SEREX Method

(1) Preparation of cDNA Library

[0109] Total RNA was prepared from testis tissue of a healthy dog by the Acid guanidium-Phenol-Chloroform method, and poly(A) RNA was purified using Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) in accordance with the protocol attached to the kit.

[0110] Using the obtained mRNA (5 μ g), a dog testis cDNA phage library was synthesized. Preparation of the cDNA phage library was carried out using cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA Gigapack III Gold Cloning Kit (manufactured by STRATAGENE) in accordance with the protocols attached to the kits. The size of the prepared cDNA phage library was 1.3×10^6 pfu/ml.

(2) Screening of cDNA Library with Serum

[0111] Using the dog testis-derived cDNA phage library prepared as described above, immunoscreening was carried out. More particularly, host *E. coli* cells (XL1-Blue MRF') were infected with the library such that 2,340 clones should appear on an NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and cultured at 42°C for 3 to 4 hours to allow the phage to form plaques. The plate was covered with nitrocellulose membrane (Hybond C Extra: manufactured by GE Healthcare Bio-Science) impregnated with IPTG (isopropyl- β -D-thiogalactoside) at 37°C for 4 hours to induce and express proteins, which were thus transferred to the membrane. Subsequently, the membrane was recovered and soaked in TBS (10 mM Tris-HCl, 150 mM NaCl; pH 7.5) containing 0.5% non-fat dry milk, followed by shaking it at 4°C overnight to suppress non-specific reactions. This filter was allowed to react with 500-fold diluted canine patient serum at room temperature for 2 to 3 hours.

[0112] As the above-described canine patient serum, serum collected from canine patients suffering from breast cancer was used. The serum was stored at -80°C and pretreated immediately before use. The method of the pretreatment of the serum was as follows. That is, host *E. coli* cells (XL1-Blue MRF') were infected with λ ZAP Express phage to which no foreign gene was inserted, and then cultured on NZY plate medium at 37°C overnight. Subsequently, the buffer of 0.2 M NaHCO₃, pH 8.3 containing 0.5 M NaCl was added to the plate, and the plate was left to stand at 4°C for 15 hours, followed by collecting the supernatant as an *E. coli*/phage extract. Thereafter, the collected *E. coli*/phage extract was allowed to flow through an NHS column (manufactured by GE Healthcare Bio-Science) to immobilize proteins derived from the *E. coli*/phage thereon. The serum from the canine patients was allowed to flow through and react with this protein-immobilized column to remove antibodies adsorbed on *E. coli* and/or the phage. The serum fraction that passed through the column was 500-fold diluted with TBS containing 0.5% non-fat dry milk, and the resulting diluent was used as the material for the immunoscreening.

[0113] The membrane on which the thus treated serum and the above-described fusion protein were blotted was washed 4 times with TBS-T (0.05% Tween 20/TBS), and allowed to react with goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated: manufactured by BETHYL Laboratories) 5,000-fold diluted with TBS containing 0.5% non-fat dry milk as a secondary antibody at room temperature for 1 hour, followed by detection by the enzyme coloring reaction using the NBT/BCIP reaction solution (manufactured by Roche). Colonies at positions where a positive coloring reaction was observed were recovered from the NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and dissolved in 500 μ l of SM buffer (100 mM NaCl, 10 mM MgClSO₄, 50 mM Tris-HCl, 0.01% gelatin; pH 7.5). The screening was repeated as a second and third screening in the same manner as described above until a single coloring reaction-positive colony was obtained, thereby isolating one positive clone after screening of 30,940 phage clones reactive with IgG in the serum.

(3) Homology Search of Isolated Antigen Gene

[0114] To subject the single positive clone isolated by the above-described method to a base sequence analysis, an operation of conversion of the phage vector to a plasmid vector was carried out. More particularly, 200 μ l of a solution

prepared to contain a host *E. coli* (XL1-Blue MRF⁺) such that the absorbance OD₆₀₀ should be 1.0 was mixed with 100 μ l of a purified phage solution and further with 1 μ l of ExAssist helper phage (manufactured by STRATAGENE), and the reaction was allowed to proceed at 37°C for 15 minutes. To the reaction mixture, 3 ml of LB medium was added, and the mixture was cultured at 37°C for 2.5 to 3 hours, followed by immediate incubation in a water bath at 70°C for 20 minutes. The mixture was then centrifuged at 4°C at 1000 $\times$ g for 15 minutes, and the supernatant was recovered as a phagemid solution. Subsequently, 200 μ l of a solution prepared to contain a phagemid host *E. coli* (SOLR) such that the absorbance OD₆₀₀ should be 1.0 was mixed with 10 μ l of a purified phage solution, and the reaction was allowed to proceed at 37°C for 15 minutes. Thereafter, 50 μ l of the reaction mixture was plated on ampicillin (final concentration: 50 μ g/ml)-containing LB agar medium, and cultured at 37°C overnight. A single colony of transformed SOLR was recovered and cultured in ampicillin (final concentration: 50 μ g/ml)-containing LB medium at 37°C, followed by purification of plasmid DNA having an insert of interest using QIAGEN plasmid Miniprep Kit (manufactured by Qiagen).

[0115] The purified plasmid was subjected to an analysis of the entire sequence of the insert by the primer walking method using the T3 primer described in SEQ ID NO:5 and the T7 primer described in SEQ ID NO:6. By this sequence analysis, the gene sequence described in SEQ ID NO:25 was obtained. Using the base sequence and the amino acid sequence of this gene, homology search against known genes was carried out using a homology search program BLAST (<http://www.ncbi.nlm.nih.gov/BLAST/>). As a result, it was revealed that the obtained gene has 99% homology (which was calculated only in the overlapping region) to the *CEP* gene described in SEQ ID NO:27 in terms of base sequence and amino acid sequence, so that the gene was judged as the *CEP* gene. The human homologous factor of the canine *CEP* was human *CEP* (homology to the *CEP* gene described in SEQ ID NO:25: base sequence, 87%; amino acid sequence, 84%). The base sequence of human *CEP* is shown in SEQ ID NO:29, and the amino acid sequence thereof is shown in SEQ ID NO:30.

(4) Analysis of Expression in Each Tissue

[0116] The expression of the gene, which was obtained by the above-described method, in normal tissues and various cell lines of dog and human were investigated by the RT-PCR (Reverse Transcription-PCR) method. The reverse transcription reaction was carried out as follows. That is, total RNA was extracted from 50 to 100 mg of each tissue or 5 to 10 $\times 10^6$ cells of each cell line using TRIZOL reagent (manufactured by Invitrogen) in accordance with the protocol attached to the kit. Using this total RNA, cDNA was synthesized by Superscript First-Strand Synthesis System for RT-PCR (manufactured by Invitrogen) in accordance with the protocol attached to the kit. As the cDNAs from human normal tissues (brain, hippocampus, testis, colon and placenta), Gene Pool cDNA (manufactured by Invitrogen), QUICK-Clone cDNA (manufactured by CLONTECH) and Large-Insert cDNA Library (manufactured by CLONTECH) were used. The PCR reactions were carried out as follows using primers (described in SEQ ID NOs:31 and 32) specific to the obtained gene. That is, respective reagents and the attached buffer were mixed such that the mixture should contain 0.25 μ l of the sample prepared by the reverse transcription reaction, 2 μ M each of the above primers, 0.2 mM each of dNTP and 0.65 U of ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 25 μ l, and the reaction was carried out with 30 cycles of 94°C for 30 seconds, 55°C for 30 seconds and 72°C for 30 seconds using Thermal Cycler (manufactured by BIO RAD). The above-described gene-specific primers were those which amplify the regions of the 4582nd to 5124th bases of the base sequences of SEQ ID NOs:25 and 27 (canine *CEP* gene) and the 4610th to 5152nd bases of the base sequence of SEQ ID NO:29 (human *CEP* gene), and can be used for investigation of the expression of both the canine *CEP* gene and the human *CEP* gene. As a control for comparison, primers (described in SEQ ID NOs:9 and 10) specific to *GAPDH* were used simultaneously. As a result, as shown in Fig. 5, strong expression of the canine *CEP* gene was observed in testis among the normal dog tissues, and on the other hand, strong expression was observed in the canine breast cancer cell line. Expression of the human *CEP* gene was confirmed, as is the case with the canine *CEP* gene, only in testis among the human normal tissues, but the expression was detected in brain tumor, leukemia and esophagus cancer cells among human cancer cell lines, and especially, strong expression was observed in the leukemia cell line. Thus, the human *CEP* gene was also confirmed to be specifically expressed in testis and cancer cells.

[0117] In Fig. 5, reference numeral 1 in the ordinate indicates the expression pattern of the *CEP* gene, and reference numeral 2 indicates the expression pattern of the *GAPDH* gene as a control for comparison.

Example C-2: Preparation of Canine and Human CEPs

(1) Preparation of Recombinant Protein

[0118] Based on the gene of SEQ ID NO:25 obtained in Example C-1, a recombinant protein was prepared by the following method. Respective reagents and the attached buffer were mixed such that the mixture should contain 1 μ l of the vector that was prepared from the phagemid solution obtained in Example C-1 and was subjected to the sequence

analysis, 0.4 μ M each of two kinds of primers having *Bam*HI and *Sal*I restriction sites (described in SEQ ID NOs:33 and 34), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 50 μ l, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 5 seconds and 72°C for 7 minutes using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:26. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 7.0 kbp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0119] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *Bam*HI and *Sal*I and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with *Bam*HI and *Sal*I. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG. In the same manner, based on the gene of SEQ ID NO:27, using the canine testis cDNA as a template and two kinds of primers having *Bam*HI and *Sal*I restriction sites (SEQ ID NOs:33 and 35), a recombinant protein of the registered canine *CEP* gene was prepared. The above-described two kinds of primers were those which amplify the region of about 7.8 kbp encoding the entire amino acid sequence of SEQ ID NO:28.

[0120] Further, based on the gene of SEQ ID NO:29, a recombinant protein of the human homologous gene was prepared by the following method. Respective reagents and the attached buffer were mixed such that the mixture should contain 1 μ l of the cDNA prepared in Example C-1 whose expression could be confirmed by the RT-PCR method in various tissues/cells, 0.4 μ M each of two kinds of primers having *Bam*HI and *Sal*I restriction sites (described in SEQ ID NOs:36 and 37), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 50 μ l, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 5 seconds and 72°C for 7 minutes using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:30. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 7.0 kbp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0121] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *Bam*HI and *Sal*I and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with *Bam*HI and *Sal*I. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

(2) Purification of Recombinant Protein

[0122] The above-obtained recombinant *E. coli* cells that expressed SEQ ID NO:25, SEQ ID NO:27, and SEQ ID NO:29, respectively, were cultured in 30 μ g/ml kanamycin-containing LB medium at 37°C until the absorbance at 600 nm reached about 0.7, and then isopropyl- β -D-1-thiogalactopyranoside was added thereto such that its final concentration should be 1 mM, followed by culturing them at 30°C for 20 hours. Subsequently, the cells were collected by centrifugation at 4,800 rpm for 10 minutes. The pellet of the cells was suspended in phosphate-buffered saline and further subjected to centrifugation at 4,800 rpm for 10 minutes to wash the cells.

[0123] The cells were suspended in phosphate-buffered saline and subjected to sonication on ice. The sonicated solution of *E. coli* was centrifuged at 7000 rpm for 20 minutes to obtain the supernatant as the soluble fraction and the precipitate as the insoluble fraction. The insoluble fraction was suspended in 4% Triton X-100 solution and the resulting suspension was centrifuged at 7000 rpm for 20 minutes. This operation was repeated twice and an operation of removal of proteases was carried out. The residue was suspended in 8 M urea-containing 10 mM Tris-HCl, 100 mM phosphate buffer (hereinafter referred to as 8 M urea solution) and a protease inhibitor cocktail solution, and the resulting suspension was left to stand at 4°C for 20 hours to denature proteins.

[0124] Thereafter, the suspension was centrifuged at 7,000 rpm for 20 minutes, and the obtained soluble fraction was placed in a nickel chelate column prepared by a conventional method (carrier: Chelating Sepharose (trademark) Fast Flow (GE Health Care); column volume: 5mL; equilibration buffer: 8M urea solution), followed by leaving it to stand at 4°C overnight. The supernatant was recovered by centrifugation of this column carrier at 1,500 rpm for 5 minutes, and the column carrier was suspended in phosphate-buffered saline, followed by refilling the column with the resulting suspension. The fraction that was not adsorbed to the column was washed away with 5 column volumes of 8 M urea

solution, 10 column volumes of 0.5 M sodium chloride-containing 0.1 M acetate buffer (pH 5.0) and 10 mM imidazole-containing 20 mM phosphate buffer (pH 8.0), and elution was immediately carried out with a five-step density gradient of 100 mM-500 mM imidazole to obtain a purified fraction, which was used as the material for administration tests thereafter. The proteins of interest in respective eluted fractions were confirmed by Coomassie staining carried out according to a conventional method. Among these, the recombinant canine CEP described in SEQ ID NO:26 is shown in Fig. 6.

[0125] To 1 ml of a reaction buffer (20 mM Tris-HCl, 50 mM NaCl, 2 mM CaCl_2 ; pH 7.4), 200 μl of the purified preparation obtained by the above-described method was aliquoted, and 2 μl of enterokinase (manufactured by Novagen) was then added thereto, followed by leaving it to stand at room temperature overnight to cleave His tag. The resulting product was purified using Enterokinase Cleavage Capture Kit (manufactured by Novagen) in accordance with the protocol attached to the kit. Subsequently, the buffer contained in 1.2 ml of the purified preparation obtained by the above-described method was replaced with physiological phosphate buffer (manufactured by Nissui Pharmaceutical) by ultra-filtration using NANOSEP 10K OMEGA (manufactured by PALL), and the resulting solution was filtered aseptically using HT Tuffryn Acrodisc 0.22 μm (manufactured by PALL) and used in the following experiments.

Example C-3: Test of Administration of Recombinant Protein to Cancer-bearing Dogs

(1) Antitumor Assay

[0126] The anti-tumor effect of the two kinds of recombinant proteins which were purified as described above was assessed in two individuals of cancer-bearing dogs having epidermal tumor (2 individuals having perianal adenoma).

[0127] An equal amount of Freund's incomplete adjuvant (manufactured by Wako Pure Chemicals) was mixed with 100 μg (0.5 ml) each of the recombinant canine CEP described in SEQ ID NO:26 and human CEP purified as described above to prepare therapeutic agents for a cancer(s). Each of these agents was administered to a regional lymph node in the vicinity of the tumor a total of 3 times, by carrying out the subsequent administrations 3 days and 7 days after the first administration. As a result, the tumors with a size of about 87 mm^3 and 69 mm^3 at the time of administration of the therapeutic agents, respectively, were reduced to 69 mm^3 and 56 mm^3 , respectively, 10 days after the first administration; 24 mm^3 and 31 mm^3 , respectively, 20 days after the first administration; and to 10 mm^3 and 8 mm^3 , respectively, 30 days after the first administration of the therapeutic agent.

[0128] Further, to a canine patient suffering from mammary adenocarcinoma, a mixture of 100 μg (0.5 ml) of the canine CEP protein described in SEQ ID NO:26 with 0.5 ml of Freund's incomplete adjuvant was administered a total of 3 times in the same manner as described above. Further, concurrently with the respective administrations, 10 MU of "Inter-cat" which is a recombinant feline interferon was administered subcutaneously. As a result, the tumor with a size of about 126 mm^3 at the time of administration of the therapeutic agent completely regressed 26 days after the first administration of the therapeutic agent. Similarly, in the case where the canine CEP described in SEQ ID NO:28 was used, an anti-tumor effect was also observed in a cancer-bearing dog.

[0129] Further, to a canine patient of mastocytoma, a mixture of 100 μg (0.5 ml) of the canine CEP protein described in SEQ ID NO:26 with 0.5 ml of Freund's incomplete adjuvant was administered a total of 3 times in the same manner as described above. Further, concurrently with the respective administrations, 100 μg of canine interleukin-12 was subcutaneously administered. As a result, the tumor with a size of about 83 mm^3 at the time of administration of the therapeutic agent completely regressed 18 days after the first administration of the therapeutic agent.

(2) Immune Inducibility Assay

[0130] Blood from the canine patient suffering from perianal adenoma in which the anti-tumor effect was obtained in the administration test in the above-described (1) was collected before administration of the therapeutic agent for a cancer(s) and 10 days and 30 days after the first administration. Peripheral blood mononuclear cells were isolated according to a conventional method, and by the ELISPOT assay for $\text{IFN}\gamma$ using it, the immune inducibility of each administered protein was assayed.

[0131] In a 96-well plate manufactured by Millipore (MultiScreen-IP, MAIPS 4510), 100 μL /well of 70% ethanol was placed and the plate was left to stand for 5 minutes, followed by removal of the ethanol by aspiration. The plate was washed with sterile water and 300 μL /well of 200 mM Sodium Bicarbonate (pH8.2) was placed therein. After leaving it to stand for 5 minutes, Sodium Bicarbonate was removed by aspiration, and then the plate was washed. Subsequently, 0.5 μL /well of anti-canine interferon γ monoclonal antibody (manufactured by R&D, clone 142529, MAB781) mixed with 200 mM Sodium Bicarbonate was placed in wells, and the plate was incubated at 37°C overnight to immobilize the primary antibody. After removal of the primary antibody by aspiration, 300 μL /well of a blocking solution (1% BSA-5% sucrose-200 mM Sodium Bicarbonate (pH8.2)) was added to the wells, and the plate was incubated at 4°C overnight to block the plate. After removal of the blocking solution by aspiration, 300 μL /well of 10% fetal calf serum-containing

RPMI medium (manufactured by Invitrogen) was placed in the wells, and the plate was left to stand for 5 minutes, followed by removal of the medium by aspiration. Subsequently, 5×10^5 cells/well of the canine peripheral blood mononuclear cells suspended in 10% fetal calf serum-containing RPMI medium were placed in the plate, and 10 μ L/well of the canine CEP described in SEQ ID NO:26 or the human CEP used in each administration was added thereto, followed by culturing the cells under the conditions of 37°C and 5% CO₂ for 24 hours, to allow immunocytes that might exist in the peripheral blood mononuclear cells to produce interferon γ . After the culture, the medium was removed, and the wells were washed 6 times with a washing solution (0.1% Tween20-200 mM Sodium Bicarbonate (pH8.2)). In each well, 100 μ L of rabbit anti-canine polyclonal antibody 1000-fold diluted with the above-described blocking solution was placed, and the plate was incubated at 4°C overnight. After washing the wells 3 times with the above-described washing solution, 100 μ L of HRP-labeled anti-rabbit antibody 1000-fold diluted with the above-described blocking solution was placed in each well, and the reaction was allowed to proceed at 37°C for 2 hours. After washing the wells 3 times with the above-described washing solution, the resultant was colored with Konica Immunostain (manufactured by Konica), and the wells were washed with water to stop the reaction. Thereafter, the membrane was dried, and image processing of the wells was carried out, followed by counting the number of spot-forming cells (SFC) using KS ELISPOT compact system (Carl Zeiss, Inc., Germany).

[0132] As a result, in either canine patient to which the canine CEP described in SEQ ID NO: 26 or the human CEP was administered, peripheral blood mononuclear cells sampled before the administration showed no spots. On the other hand, in the canine patient to which the canine CEP was administered, peripheral blood mononuclear cells sampled 10 days and 30 days after the administration showed 23 and 52 spots, respectively. In the canine patient to which the human CEP was administered, peripheral blood mononuclear cells sampled 10 days and 30 days after the administration showed 19 and 49 spots, respectively.

[0133] From the above results, it is confirmed that immunocytes which specifically react with the administered recombinant protein and produce interferon γ were induced in all of the canine patients to which the recombinant protein was administered, and it is thought that the anti-tumor effect described in (1) was exerted by immunoreactions in which these immunocytes are mainly involved.

Example D-1: Acquisition of Novel Cancer Antigen Protein by SEREX Method

(1) Preparation of cDNA Library

[0134] Total RNA was prepared from testis tissue of a healthy dog by the Acid guanidium-Phenol-Chloroform method, and poly(A) RNA was purified using Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) in accordance with the protocol attached to the kit.

[0135] Using the obtained mRNA (5 μ g), a dog testis cDNA phage library was synthesized. Preparation of the cDNA phage library was carried out using cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA Gigapack III Gold Cloning Kit (manufactured by STRATAGENE) in accordance with the protocols attached to the kits. The size of the prepared cDNA phage library was 1.3×10^6 pfu/ml.

(2) Screening of cDNA Library with Serum

[0136] Using the dog testis-derived cDNA phage library prepared as described above, immunoscreening was carried out. More particularly, host *E. coli* cells (XL1-Blue MRF') were infected with the library such that 2,340 clones should appear on an NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and cultured at 42°C for 3 to 4 hours to allow the phage to form plaques. The plate was covered with nitrocellulose membrane (Hybond C Extra: manufactured by GE Healthcare Bio-Science) impregnated with IPTG (isopropyl- β -D-thiogalactoside) at 37°C for 4 hours to induce and express proteins, which were thus transferred to the membrane. Subsequently, the membrane was recovered and soaked in TBS (10 mM Tris-HCl, 150 mM NaCl; pH 7.5) containing 0.5% non-fat dry milk, followed by shaking at 4°C overnight to suppress non-specific reactions. This filter was allowed to react with 500-fold diluted canine patient serum at room temperature for 2 to 3 hours.

[0137] As the above-described canine patient serum, serum collected from canine patients suffering from breast cancer was used. The serum was stored at -80°C and pretreated immediately before use. The method of the pretreatment of the serum was as follows. That is, host *E. coli* cells (XL1-Blue MRF') were infected with λ , ZAP Express phage to which no foreign gene was inserted, and then cultured on NZY plate medium at 37°C overnight. Subsequently, the buffer of 0.2 M NaHCO₃, pH 8.3 containing 0.5 M NaCl was added to the plate, and the plate was left to stand at 4°C for 15 hours, followed by collecting the supernatant as an *E. coli*/phage extract. Thereafter, the collected *E. coli*/phage extract was allowed to flow through an NHS column (manufactured by GE Healthcare Bio-Science) to immobilize proteins derived from the *E. coli*/phage thereon. The serum from the canine patients was allowed to flow through and react with this protein-immobilized column to remove antibodies adsorbed on *E. coli* and/or the phage. The serum fraction that passed

through the column was 500-fold diluted with TBS containing 0.5% non-fat dry milk, and the resulting diluent was used as the material for the immunoscreening.

[0138] The membrane on which the thus treated serum and the above-described fusion protein were blotted was washed 4 times with TBS-T (0.05% Tween 20/TBS), and allowed to react with goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated: manufactured by BETHYL Laboratories) 5,000-fold diluted with TBS containing 0.5% non-fat dry milk as a secondary antibody at room temperature for 1 hour, followed by detection by the enzyme coloring reaction using the NBT/BCIP reaction solution (manufactured by Roche). Colonies at positions where a positive coloring reaction was observed were recovered from the NZY agarose plate having the size of $\Phi 90 \times 15$ mm, and dissolved in 500 μ l of SM buffer (100 mM NaCl, 10 mM MgClSO₄, 50 mM Tris-HCl, 0.01% gelatin; pH 7.5). The screening was repeated as a second and third screening in the same manner as described above until a single coloring reaction-positive colony was obtained, thereby isolating one positive clone after screening of 30,940 phage clones reactive with IgG in the serum.

(3) Homology Search of Isolated Antigen Gene

[0139] To subject the single positive clone isolated by the above-described method to a base sequence analysis, an operation of conversion of the phage vector to a plasmid vector was carried out. More particularly, 200 μ l of a solution prepared to contain a host *E. coli* (XL1-Blue MRF⁺) such that the absorbance OD₆₀₀ should be 1.0 was mixed with 100 μ l of a purified phage solution and further with 1 μ l of ExAssist helper phage (manufactured by STRATAGENE), and the reaction was allowed to proceed at 37°C for 15 minutes. To the reaction mixture, 3 ml of LB medium was added, and the mixture was cultured at 37°C for 2.5 to 3 hours, followed by immediate incubation in a water bath at 70°C for 20 minutes. The mixture was then centrifuged at 4°C at 1000 xg for 15 minutes, and the supernatant was recovered as a phagemid solution. Subsequently, 200 μ l of a solution prepared to contain a phagemid host *E. coli* (SOLR) such that the absorbance OD₆₀₀ should be 1.0 was mixed with 10 μ l of a purified phage solution, and the reaction was allowed to proceed at 37°C for 15 minutes. Thereafter, 50 μ l of the reaction mixture was plated on ampicillin (final concentration: 50 μ g/ml)-containing LB agar medium, and cultured at 37°C overnight. A single colony of transformed SOLR was recovered and cultured in ampicillin (final concentration: 50 μ g/ml)-containing LB medium at 37°C, followed by purification of plasmid DNA having an insert of interest using QIAGEN plasmid Miniprep Kit (manufactured by Qiagen).

[0140] The purified plasmid was subjected to an analysis of the entire sequence of the insert by the primer walking method using the T3 primer described in SEQ ID NO:5 and the T7 primer described in SEQ ID NO:6. By this sequence analysis, the gene sequence described in SEQ ID NO:38 was obtained. Using the base sequence and the amino acid sequence of this gene, homology search against known genes was carried out using a homology search program BLAST (<http://www.ncbi.nlm.nih.gov/BLAST/>). As a result, it was revealed that the obtained gene is the *TRIP11* gene. The human homologous factor of canine *TRIP11* was human *TRIP11* (homology: base sequence, 88%; amino acid sequence, 86%). The base sequence of human *TRIP11* is shown in SEQ ID NO:40, and the amino acid sequence thereof is shown in SEQ ID NO:41.

(4) Analysis of Expression in Each Tissue

[0141] The expression of the gene, which was obtained by the above-described method, in normal tissues and various cell lines of dog and human were investigated by the RT-PCR (Reverse Transcription-PCR) method. The reverse transcription reaction was carried out as follows. That is, total RNA was extracted from 50 to 100 mg of each tissue or 5 to 10 $\times 10^6$ cells of each cell line using TRIzol reagent (manufactured by Invitrogen) in accordance with the protocol attached to the kit. Using this total RNA, cDNA was synthesized by Superscript First-Strand Synthesis System for RT-PCR (manufactured by Invitrogen) in accordance with the protocol attached to the kit. As the cDNAs from human normal tissues (brain, hippocampus, testis, colon and placenta), Gene Pool cDNA (manufactured by Invitrogen), QUICK-Clone cDNA (manufactured by CLONTECH) and Large-Insert cDNA Library (manufactured by CLONTECH) were used. The PCR reactions were carried out as follows using primers (described in SEQ ID NOs:42 and 43) specific to the obtained gene. That is, respective reagents and the attached buffer were mixed such that the mixture should contain 0.25 μ l of the sample prepared by the reverse transcription reaction, 2 μ M each of the above primers, 0.2 mM each of dNTP and 0.65 U of ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 25 μ l, and the reaction was carried out with 30 cycles of 94°C for 30 seconds, 55°C for 30 seconds and 72°C for 1.5 minutes using Thermal Cycler (manufactured by BIO RAD). The above-described gene-specific primers were those which amplify the regions of the 1519th to 2957th bases of the base sequence of SEQ ID NO:38 (canine *TRIP11* gene) and the 1872nd to 3310th bases of the base sequence of SEQ ID NO:40 (human *TRIP11* gene), and can be used for investigation of the expression of both the canine *TRIP11* gene and the human *TRIP11* gene. As a control for comparison, primers (described in SEQ ID NOs:9 and 10) specific to GAPDH were used simultaneously. As a result, as shown in Fig. 7, strong expression of the canine *TRIP 11* gene was observed in testis among the normal dog tissues, and on the other hand, strong expression was observed in the canine breast cancer cell line. Expression of the human gene was confirmed, as is the case with

the canine *TRIP11* gene, only in testis among the human normal tissues, but the expression was detected in many types of cancer cell lines such as brain tumor, leukemia, breast cancer, lung cancer and esophagus cancer cell lines among human cancer cell lines. Thus, the human *TRIP11* gene was also confirmed to be specifically expressed in testis and cancer cells.

[0142] In Fig. 7, reference numeral 1 in the ordinate indicates the expression pattern of the *TRIP11* gene, and reference numeral 2 indicates the expression pattern of the *GAPDH* gene as a control for comparison.

Example D-2: Preparation of Canine and Human TRIP 11 Proteins

(1) Preparation of Recombinant Protein

[0143] Based on the gene of SEQ ID NO:38 obtained in Example D-1, a recombinant protein was prepared by the following method. NO:Respective reagents and the attached buffer were mixed such that the mixture should contain 1 μ l of the vector which was prepared from the phagemid solution obtained in Example D-1 and was subjected to the sequence analysis, 0.4 μ M each of two kinds of primers having *Sall* and *XhoI* restriction sites (described in SEQ ID NOs:44 and 45), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 50 μ l, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 5 seconds and 72°C for 6 minutes using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:39. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 6.0 kbp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0144] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *Sall* and *XhoI* and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30b (manufactured by Novagen) that had been treated with *Sall* and *XhoI*. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

[0145] Further, based on the gene of SEQ ID NO:40, a recombinant protein of the human homologous gene was prepared by the following method. Respective reagents and the attached buffer were mixed such that the mixture should contain 1 μ l of the cDNA prepared in Example D-1 whose expression could be confirmed by the RT-PCR method in various tissues/cells, 0.4 μ M each of two kinds of primers having *NdeI* and *KpnI* restriction sites (described in SEQ ID NOs:46 and 47), 0.2 mM dNTP and 1.25 U of PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) in a total volume of 50 μ l, and PCR was carried out with 30 cycles of 98°C for 10 seconds, 55°C for 5 seconds and 72°C for 6 minutes using Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those which amplify the region encoding the entire amino acid sequence of SEQ ID NO:41. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 6.0 kbp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0146] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the amplified gene fragment matches the sequence of interest. The plasmid that matched the sequence of interest was treated with restriction enzymes *NdeI* and *KpnI* and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30b (manufactured by Novagen) that had been treated with *NdeI* and *KpnI*. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

(2) Purification of Recombinant Proteins

[0147] The above-obtained recombinant *E. coli* cells that expressed SEQ ID NO:38 and SEQ ID NO:40, respectively, were cultured in 30 μ g/ml kanamycin-containing LB medium at 37°C until the absorbance at 600 nm reached about 0.7, and then isopropyl- β -D-1-thiogalactopyranoside was added thereto such that its final concentration should be 1 mM, followed by culturing them at 30°C for 20 hours. Subsequently, the cells were collected by centrifugation at 4,800 rpm for 10 minutes. The pellet of the cells was suspended in phosphate-buffered saline and further subjected to centrifugation at 4,800 rpm for 10 minutes to wash the cells.

[0148] The obtained pellet of *E. coli* cells was suspended in phosphate-buffered saline and subjected to sonication on ice. The sonicated solution of *E. coli* was centrifuged at 7,000 rpm for 15 minutes to obtain the supernatant as the

soluble fraction and the precipitate as the insoluble fraction.

[0149] The insoluble fraction was suspended in 4% Triton X-100 solution and the resulting suspension was centrifuged at 7,000 rpm for 10 minutes. This operation was repeated twice and an operation of removal of proteases was carried out. Thereafter, the residue was suspended in phosphate-buffered saline and an operation of removal of the surfactant was carried out.

[0150] The residue was suspended in 6M guanidine hydrochloride-containing 20 mM phosphate buffer (pH 8.0), and the resulting suspension was left to stand at 4°C for 20 hours to denature proteins. Thereafter, the suspension was centrifuged at 7,000 rpm for 20 minutes, and the obtained soluble fraction was placed in a nickel chelate column prepared by a conventional method (carrier: Chelating Sepharose (trademark) Fast Flow (GE Health Care); column volume: 5mL; equilibration buffer: 6M guanidine hydrochloride-containing 20 mM phosphate buffer (pH 8.0)). The fraction that was not adsorbed to the column was washed away with 10 column volumes of 6 M sodium chloride-containing 20 mM phosphate buffer (pH 8.0) and 10 mM imidazole-containing 20 mM phosphate buffer (pH 8.0), and elution was immediately carried out with a four-step density gradient of 50 mM-500 mM imidazole to obtain a purified fraction, which was used as the material for administration tests thereafter. The proteins of interest in the eluted fractions were confirmed by Coomassie staining carried out according to a conventional method. Among these, the canine TRIP11 protein is shown in Fig. 8.

[0151] To 1 ml of a reaction buffer (20 mM Tris-HCl, 50 mM NaCl, 2 mM CaCl_2 ; pH 7.4), 200 μl of the purified preparation obtained by the above-described method was aliquoted, and 2 μl of enterokinase (manufactured by Novagen) was then added thereto, followed by leaving it to stand at room temperature overnight to cleave His tag. The resulting product was purified using Enterokinase Cleavage Capture Kit (manufactured by Novagen) in accordance with the protocol attached to the kit. Subsequently, the buffer contained in 1.2 ml of the purified preparation obtained by the above-described method was replaced with physiological phosphate buffer (manufactured by Nissui Pharmaceutical) by ultra-filtration using NANOSEP 10K OMEGA (manufactured by PALL), and the resulting solution was filtered aseptically using HT Tuffryn Acrodisc 0.22 μm (manufactured by PALL) and used in the following experiments.

Example D-3: Test of Administration of Recombinant Protein to Cancer-bearing Dogs

(1) Antitumor Assay

[0152] The anti-tumor effect of the two kinds of recombinant proteins which were purified as described above was assessed in two individuals of cancer-bearing dogs having epidermal tumor (2 individuals having mammary gland tumor).

[0153] Therapeutic agents for a cancer(s) were prepared by mixing 0.5 ml of Freund's incomplete adjuvant (manufactured by Wako Pure Chemicals) with 100 μg (0.5 ml) of the recombinant canine TRIP11 and human TRIP11 proteins, respectively, purified as described above. Each of these agents was administered to a regional lymph node in the vicinity of the tumor a total of 3 times, by carrying out the subsequent administrations 3 days and 7 days after the first administration. As a result, the tumors with a size of about 75 mm^3 and 102 mm^3 , respectively, at the time of administration of the therapeutic agents were reduced to 63 mm^3 and 85 mm^3 , respectively, 10 days after the first administration; 35 mm^3 and 42 mm^3 , respectively, 20 days after the first administration; and to 15 mm^3 and 19 mm^3 , respectively, 30 days after the first administration of the therapeutic agent for a cancer(s).

[0154] Further, to a canine patient suffering from mastocytoma, a mixture of 100 μg (0.5 ml) of the canine TRP11 protein with 0.5 ml of Freund's incomplete adjuvant was administered a total of 3 times in the same manner as described above. Concurrently with the respective administrations, 100 μg of canine interleukin-12 was subcutaneously administered. As a result, the tumor with a size of about 165 mm^3 at the time of administration of the therapeutic agent completely regressed 23 days after the first administration of the therapeutic agent.

(2) Immune Inducibility Assay

[0155] Blood from the canine patient suffering from mammary gland tumor in which the anti-tumor effect was obtained in the administration test in the above-described (1) was collected. Peripheral blood mononuclear cells were isolated according to a conventional method, and by the ELISPOT assay for $\text{IFN}\gamma$ using it, the immune inducibility of each administered protein was assayed.

[0156] In a 96-well plate manufactured by Millipore (MultiScreen-IP, MAIPS 4510), 100 μL /well of 70% ethanol was placed and the plate was left to stand for 5 minutes, followed by removal of the ethanol by aspiration. The plate was washed with sterile water and 300 μL /well of 200 mM Sodium Bicarbonate (pH8.2) was placed therein. After leaving it to stand for 5 minutes, Sodium Bicarbonate was removed by aspiration, and then the plate was washed. Subsequently, 0.5 μg /well of anti-canine interferon γ monoclonal antibody (manufactured by R&D, clone 142529, MAB781) mixed with 200 mM Sodium Bicarbonate was placed in wells, and the plate was incubated at 37°C overnight to immobilize the primary antibody. After removal of the primary antibody by aspiration, 300 μL /well of a blocking solution (1% BSA-5% sucrose-200 mM Sodium Bicarbonate (pH8.2)) was added to the wells, and the plate was incubated at 4°C overnight

to block the plate. After removal of the blocking solution by aspiration, 300 μ L/well of 10% fetal calf serum-containing RPMI medium (manufactured by Invitrogen) was placed in the wells and the plate was left to stand for 5 minutes, followed by removal of the medium by aspiration. Subsequently, 5×10^5 cells/well of the canine peripheral blood mononuclear cells suspended in 10% fetal calf serum-containing RPMI medium were placed in the plate, and 10 μ L/well of the canine TRIP 11 or the human TRIP 11 protein used in each administration was added thereto, followed by culturing the cells under the conditions of 37°C and 5% CO₂ for 24 hours, to allow immunocytes that might exist in the peripheral blood mononuclear cells to produce interferon γ . After the culture, the medium was removed, and the wells were washed 6 times with a washing solution (0.1% Tween20-200mM Sodium Bicarbonate (pH8.2)). In each well, 100 μ L of rabbit anti-dog polyclonal antibody 1000-fold diluted with the above-described blocking solution was placed, and the plate was incubated at 4°C overnight. After washing the wells 3 times with the above-described washing solution, 100 μ L of HRP-labeled anti-rabbit antibody 1,000-fold diluted with the above-described blocking solution was placed in each well, and the reaction was allowed to proceed at 37°C for 2 hours. After washing the wells 3 times with the above-described washing solution, the resultant was colored with Konica Immunostain (manufactured by Konica), and the wells were washed with water to stop the reaction. Thereafter, the membrane was dried, and image processing of the wells was carried out, followed by counting the number of spot-forming cells (SFC) using KS ELISPOT compact system (Carl Zeiss, Inc., Germany).

[0157] As a result, in either canine patient to which the canine TRIP11 protein or the human TRIP11 protein was administered, peripheral blood mononuclear cells sampled before the administration showed no spots. On the other hand, in the canine patient to which the canine TRIP11 was administered, peripheral blood mononuclear cells sampled 10 days and 30 days after the administration showed 26 and 65 spots, respectively. In the canine patient to which the human TRIP11 was administered, peripheral blood mononuclear cells sampled 10 days and 30 days after the administration showed 31 and 72 spots, respectively.

[0158] From the above results, it is confirmed that immunocytes which specifically react with the administered recombinant protein and produce interferon γ were induced in all of the canine patients to which the recombinant protein was administered, and it is thought that the anti-tumor effect described in the above-described (1) was exerted by immunoreactions in which these immunocytes are mainly involved.

[0159] The following numbered paragraphs (paras.) contain further statements of various aspects of the present invention:-

1. An immunity-inducing agent comprising as an effective ingredient any one of the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity, or as an effective ingredient a recombinant vector which comprises a polynucleotide encoding said polypeptide and is capable of expressing said polypeptide *in vivo*:

(a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING;

(b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and

(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

2. The immunity-inducing agent according to para. 1, wherein said polypeptide (b) has a homology of not less than 95% to said polypeptide (a).

3. The immunity-inducing agent according to para. 1, wherein said polypeptide having an immunity-inducing activity is a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING or a polypeptide comprising said polypeptide as a partial sequence thereof.

4. The immunity-inducing agent according to para.3, wherein said polypeptide having an immunity-inducing activity has the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING.

5. The immunity-inducing agent according to any one of paras. 1 to 4, comprising a polypeptide as an effective ingredient.

6. The immunity-inducing agent according to para. 5, which is an agent for treating antigen-presenting cells.

7. The immunity-inducing agent according to any one of paras. 1 to 5, which is a therapeutic and/or prophylactic agent for a cancer(s).

8. The immunity-inducing agent according to para. 7, which is for humans, dogs or cats.

9. The immunity-inducing agent according to paras.7 or 8, further comprising an immunoenhancer.

10. The immunity-inducing agent according to para. 9, wherein said immunoenhancer is at least one selected from the group consisting of Freund's incomplete adjuvant; Montanide; poly I:C and derivatives thereof; CpG oligonucleotides; interleukin-12; interleukin-18; interferon- α ; interferon- β ; interferon- ω ; interferon- γ ; and Flt3 ligand.

11. A method for inducing immunity, said method comprising administering to an individual an effective amount of

any one of the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity, or an effective amount of a recombinant vector which comprises a polynucleotide encoding said polypeptide and is capable of expressing said polypeptide *in vivo*:

- 5 (a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING;
 (b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and
 (c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

10 12. A method for treating antigen-presenting cells, said method comprising bringing any one of the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity, into contact with antigen-presenting cells:

- 15 (a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING;
 (b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and
 (c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

20 13. Use of any one of the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity, or a recombinant vector which comprises a polynucleotide encoding said polypeptide and is capable of expressing said polypeptide *in vivo*, for production of an immunity-inducing agent:

- 25 (a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO:2, 4, 16, 18, 26, 28, 30, 39 or 41 in SEQUENCE LISTING;
 (b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and
 (c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

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EP 3 192 523 A1

SEQUENCE LISTING

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<140> Divisional application of: EP 08840900.8

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Ser Ser His Ser Pro Ser Pro Pro Ser Leu Thr Ser Asn Met Arg Ser
20 25 30

agg tca ctt tcg cct cta agt gga tct gag act ctg cct ttt cat ttt 144
Arg Ser Leu Ser Pro Leu Ser Gly Ser Glu Thr Leu Pro Phe His Phe
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Gly Gly Pro Trp His Glu Gln Val Glu Ile Thr Asp Glu Ser Thr Val
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gtt tta gac tac caa gac cat aaa gaa gct gat tca cat gca gga gtc 240
Val Leu Asp Tyr Gln Asp His Lys Glu Ala Asp Ser His Ala Gly Val
65 70 75 80

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Arg Tyr Ile Thr Glu Ala Leu Val Arg Lys Leu Thr Lys Gln Asp Asn
85 90 95

ttg gcc ttg gta aaa tct ctg aac ctt tca ctt gct aaa ggt ggt ggc 336
Leu Ala Leu Val Lys Ser Leu Asn Leu Ser Leu Ala Lys Gly Gly Gly
100 105 110

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Lys Lys Phe Arg Cys Ile Glu Asn Leu Glu Lys Cys Val Lys Leu Glu
115 120 125

gta ctg aat ctc agc tat aat cta ata gga aag att gag aaa gtg gac 432
Val Leu Asn Leu Ser Tyr Asn Leu Ile Gly Lys Ile Glu Lys Val Asp
130 135 140

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Lys Leu Leu Lys Leu Arg Glu Leu Asn Leu Ser Tyr Asn Lys Ile Arg
145 150 155 160

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	Ala	Gly	Asn	Glu	Ile	Glu	His	Ile	Pro	Val	Trp	Leu	Gly	Lys	Lys	Leu	
				180					185					190			
10	aaa	tct	ttg	cga	atc	ctg	aat	ctg	aaa	ggc	aac	aag	ata	tca	tcg	ctc	624
	Lys	Ser	Leu	Arg	Ile	Leu	Asn	Leu	Lys	Gly	Asn	Lys	Ile	Ser	Ser	Leu	
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	caa	gat	gta	agc	aag	ttg	aaa	cca	ctt	caa	gat	ttg	act	tct	ctg	atc	672
	Gln	Asp	Val	Ser	Lys	Leu	Lys	Pro	Leu	Gln	Asp	Leu	Thr	Ser	Leu	Ile	
		210					215					220					
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	Leu	Leu	Glu	Asn	Pro	Val	Ala	Thr	Leu	Pro	His	Tyr	Ile	Gln	Phe	Thr	
	225					230					235					240	
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	Ile	Phe	His	Leu	Arg	Ser	Leu	Glu	Ser	Leu	Glu	Gly	Gln	Pro	Val	Thr	
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	Ser	Gln	Asp	Arg	Gln	Glu	Ala	Phe	Ala	Arg	Phe	Ser	Leu	Asp	Glu	Val	
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	Glu	Arg	Leu	Glu	Arg	Asp	Leu	Glu	Lys	Lys	Thr	Met	Glu	Thr	Glu	Glu	
			275					280					285				
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	Leu	Arg	Ser	Glu	Gln	Thr	Arg	Phe	Leu	Glu	Glu	Ile	Lys	Ser	Gln	Asp	
		290					295					300					
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	Lys	Leu	Asn	Lys	Ser	Leu	Lys	Glu	Glu	Ala	Arg	Leu	Gln	Lys	Gln	Ser	
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	tat	gag	gag	ctg	gag	agt	aac	cta	aac	acc	aaa	aat	gaa	ttg	cta	aaa	1008
	Tyr	Glu	Glu	Leu	Glu	Ser	Asn	Leu	Asn	Thr	Lys	Asn	Glu	Leu	Leu	Lys	
					325					330					335		
40	cag	aag	acc	atg	gaa	cta	atg	cga	gca	tgt	cag	aaa	cag	tat	gag	atg	1056
	Gln	Lys	Thr	Met	Glu	Leu	Met	Arg	Ala	Cys	Gln	Lys	Gln	Tyr	Glu	Met	
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	Glu	Gln	Glu	Leu	Ala	Phe	Tyr	Lys	Ile	Asp	Ala	Lys	Phe	Glu	Pro	Leu	
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	aat	tat	tac	cca	tca	gag	tat	gtc	gaa	att	gat	aaa	acc	cca	gat	gaa	1152
	Asn	Tyr	Tyr	Pro	Ser	Glu	Tyr	Val	Glu	Ile	Asp	Lys	Thr	Pro	Asp	Glu	
		370					375					380					
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	Ser	Pro	Tyr	Ile	Gly	Lys	Ser	Arg	Tyr	Lys	Arg	Asn	Met	Phe	Thr	Thr	
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55	gag	agt	tat	att	att	gca	aat	gcc	cag	aca	gta	aag	atc	aag	aag	atg	1248
	Glu	Ser	Tyr	Ile	Ile	Ala	Asn	Ala	Gln	Thr	Val	Lys	Ile	Lys	Lys	Met	
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[illegible]

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5	cat gag gtg aat ata tct ctg cag cag acc cag gga gat ctc agt gcc	2112
	His Glu Val Asn Ile Ser Leu Gln Gln Thr Gln Gly Asp Leu Ser Ala	
	690 695 700	
10	tat gag gct gag cta gag gct cag ctg aaa ata cgg gat gct gaa gcc	2160
	Tyr Glu Ala Glu Leu Glu Ala Gln Leu Lys Ile Arg Asp Ala Glu Ala	
	705 710 715 720	
15	aac cag ctc aag gag gag ttg gaa aaa ctt aga agg ttg agc cag tta	2208
	Asn Gln Leu Lys Glu Glu Leu Glu Lys Leu Arg Arg Leu Ser Gln Leu	
	725 730 735	
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	Glu Gln Ser Ala Leu Gln Ala Glu Leu Glu Lys Glu Lys Gln Ala Phe	
	740 745 750	
25	aag act gct gtc aaa aaa gcc cag ctc tca gaa gga aag gac caa gaa	2304
	Lys Thr Ala Val Lys Lys Ala Gln Leu Ser Glu Gly Lys Asp Gln Glu	
	755 760 765	
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	770 775 780	
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	Val Asp Gly Leu Ile Arg Pro Glu Glu Val Ala Ala Cys Val Asp Glu	
	805 810 815	
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	Leu Arg Lys Lys Leu Lys Ser Gly Ala Gly Glu Met Arg Ile His Thr	
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	Ser Glu Ile Leu Ala Arg Ser Gln Trp Glu Arg Gln Glu Ala Gln Val	
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	Ala Ser Gly Gln Glu Glu Phe Arg His Ala Cys Glu Arg Ala Leu Glu	
	885 890 895	
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	Ala Arg Ile Ser Phe Asp Lys Arg Gln His Glu Ala Arg Ile Gln Gln	
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	Leu Glu Asn Glu Ile His Tyr Leu Gln Glu Asn Leu Lys Ser Met Glu	

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	aag gag aga att ctg gcc Lys Glu Arg Ile Leu Ala 945	caa ctc cgg gag tta Gln Leu Arg Glu Leu 950	gag aaa aag aag aaa Glu Lys Lys Lys Lys 955 960	2880
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	Asp	Gln	Glu	Asp	His	Pro	Phe	Val	Pro	Pro	Pro	Gly	Tyr	Met	Met	
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	Tyr	Thr	Val	Phe	Pro	Asp	Gly	Ser	Pro	Val	Pro	Gln	Gly	Met	Ala	
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	Leu	Tyr	Ala	Pro	Pro	Pro	Pro	Leu	Pro	Asn	Asn	Ser	Gln	Pro	Leu	
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	Ile	Val	Tyr	Gly	Pro	Pro	Pro	Pro	Asn	Phe	Ser	Val	Pro	Leu	Ile	
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	Asn Leu Gln Val Val Leu Gly Gln Met Ser Lys His Lys Thr Glu	
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	Gln Gly Leu Lys Leu Gln His Asp Gln Lys Met Ser Glu Leu Glu	
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	Lys Thr Arg Val Glu Val Leu Glu Glu Lys Leu Glu Leu Glu Ser	
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	Leu Gln Gln Ala Ala Leu Arg Gln Arg Gly Glu Ile Glu Trp Gln	
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40	aag cag ctc ctc cag agg aac aca cag gaa gta gag cgg atg act	5319
	Lys Gln Leu Leu Gln Arg Asn Thr Gln Glu Val Glu Arg Met Thr	
	1760 1765 1770	
45	gct gag acc cga gca tta cag tcg tgt gtt gag tct ttg tgc aaa	5364
	Ala Glu Thr Arg Ala Leu Gln Ser Cys Val Glu Ser Leu Cys Lys	
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	Glu Lys Gln Asp Leu Glu Glu Lys Gln Asp Ser Trp Glu Lys Lys	
	1790 1795 1800	
55	ttg gca cag acc aaa cgg gtt cta gca gct gca gaa gag gac agc	5454
	Leu Ala Gln Thr Lys Arg Val Leu Ala Ala Ala Glu Glu Asp Ser	
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	Glu Met Glu Arg Ala Arg Leu Glu Lys Leu Glu Leu Asp Ala Arg	
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	Leu His Gln Asp Leu Ala Val Val Gln Gln Gln Leu Gln Glu Lys	
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75	cag gaa gca gta aac tca tta cag aag gaa cta act gat gtc cag	5634
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	Glu	His	Leu	Asp	Leu	Ala	Glu	Gln	Glu	Val	Leu	Cys	Thr	Thr	Lys	
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	Arg	Lys	Asp	Ala	Leu	Leu	Ser	Glu	Gln	Thr	Arg	Leu	Glu	Lys	Asp	
	1895				1900				1905							
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	Val	Gly	Glu	Trp	Thr	Lys	Lys	Phe	Glu	Asp	Cys	Gln	Lys	Glu	Gly	
	1910				1915				1920							
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	Glu	Thr	Lys	Gln	Gln	Gln	Leu	Gln	Gly	Leu	Gln	Lys	Glu	Ile	Glu	
	1925				1930				1935							
25	gga	aac	gag	gcg	aag	cta	gcc	caa	caa	gaa	atg	atg	ttt	cag	aga	5859
	Gly	Asn	Glu	Ala	Lys	Leu	Ala	Gln	Gln	Glu	Met	Met	Phe	Gln	Arg	
	1940				1945				1950							
30	ctc	cag	aaa	gag	cga	gaa	tgt	gaa	gaa	aaa	aag	tta	gaa	gct	agt	5904
	Leu	Gln	Lys	Glu	Arg	Glu	Cys	Glu	Glu	Lys	Lys	Leu	Glu	Ala	Ser	
	1955				1960				1965							
35	aaa	gtg	act	ctg	aag	gag	cag	cag	caa	cag	ctg	gaa	aag	gaa	ttg	5949
	Lys	Val	Thr	Leu	Lys	Glu	Gln	Gln	Gln	Gln	Leu	Glu	Lys	Glu	Leu	
	1970				1975				1980							
40	atg	gag	cag	aaa	ggc	aag	ctg	gac	cag	gtg	ctc	gct	aag	ctc	ttg	5994
	Met	Glu	Gln	Lys	Gly	Lys	Leu	Asp	Gln	Val	Leu	Ala	Lys	Leu	Leu	
	1985				1990				1995							
45	gtg	gct	gag	gag	cgt	gtc	agg	acc	ttg	cag	gag	gag	gga	agg	tgg	6039
	Val	Ala	Glu	Glu	Arg	Val	Arg	Thr	Leu	Gln	Glu	Glu	Gly	Arg	Trp	
	2000				2005				2010							
50	agc	gag	acc	ctg	gag	aag	acg	ctc	tcc	cag	acc	aag	cga	cag	ctt	6084
	Ser	Glu	Thr	Leu	Glu	Lys	Thr	Leu	Ser	Gln	Thr	Lys	Arg	Gln	Leu	
	2015				2020				2025							
55	tca	gaa	cgg	gag	cag	cag	tta	ctg	gcc	aag	tca	gac	gag	ctg	ctg	6129
	Ser	Glu	Arg	Glu	Gln	Gln	Leu	Leu	Ala	Lys	Ser	Asp	Glu	Leu	Leu	
	2030				2035				2040							
60	gcc	ctg	cag	aag	gag	acg	gac	tcc	atg	agg	gcg	gac	ttc	agc	ctc	6174
	Ala	Leu	Gln	Lys	Glu	Thr	Asp	Ser	Met	Arg	Ala	Asp	Phe	Ser	Leu	
	2045				2050				2055							
65	ttg	cgc	aac	cag	ttc	ctg	aca	gaa	aga	aag	aaa	gcc	gag	aag	cag	6219
	Leu	Arg	Asn	Gln	Phe	Leu	Thr	Glu	Arg	Lys	Lys	Ala	Glu	Lys	Gln	
	2060				2065				2070							
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	Val	Ala	Ser	Leu	Lys	Glu	Ala	Leu	Lys	Ile	Gln	Arg	Ser	Gln	Leu	
	2075				2080				2085							
75	gag	aag	aac	ctt	ctg	gag	caa	aag	cag	gag	aac	agc	tgc	atg	cag	6309
	Glu	Lys	Asn	Leu	Leu	Glu	Gln	Lys	Gln	Glu	Asn	Ser	Cys	Met	Gln	
	2090				2095				2100							
80	agg	gag	atg	gca	acc	atc	gaa	cag	gtg	gcc	cag	gac	aac	cac	gag	6354

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5	cgg	gcc	cgg	cgc	cta	atg	agg	gag	ctc	aac	cag	atg	cag	cgc	gag	6399
	Arg	Ala	Arg	Arg	Leu	Met	Arg	Glu	Leu	Asn	Gln	Met	Gln	Arg	Glu	
	2120						2125					2130				
10	tac	gtg	gag	ctc	agg	aaa	cag	atg	aca	aac	caa	aag	gat	ttg	gaa	6444
	Tyr	Val	Glu	Leu	Arg	Lys	Gln	Met	Thr	Asn	Gln	Lys	Asp	Leu	Glu	
	2135						2140					2145				
	aga	aga	cag	atg	gaa	atc	agt	gat	gcg	atg	caa	gca	ctt	aaa	tgt	6489
	Arg	Arg	Gln	Met	Glu	Ile	Ser	Asp	Ala	Met	Gln	Ala	Leu	Lys	Cys	
	2150						2155					2160				
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	Glu	Val	Lys	Asp	Glu	Ile	Arg	Thr	Ser	Leu	Lys	Asn	Leu	Asn	Gln	
	2165						2170					2175				
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	Phe	Leu	Pro	Glu	Leu	Pro	Ala	Asp	Leu	Glu	Ala	Leu	Leu	Glu	Arg	
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25	ccg	ttt	acc	gtg	agc	gac	aga	cca	tca	tct	tgc	gaa	gag	aaa	ctg	6669
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	Ala	Leu	Arg	Glu	Lys	Leu	Arg	His	Arg	Glu	Asp	Arg	Leu	Lys	Ala	
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	Gln	Leu	Arg	Arg	Cys	Met	Ser	Lys	Gln	Ala	Glu	Val	Leu	Ser	Glu	
	2255						2260					2265				
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	Gly	Arg	Arg	Arg	Thr	Glu	Gly	Thr	Leu	His	Ser	Leu	Arg	Arg	Gln	
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45	gtg	gac	gcc	ctg	ggc	gag	ctg	gtc	acc	agc	act	tcc	ggg	gac	tcc	6894
	Val	Asp	Ala	Leu	Gly	Glu	Leu	Val	Thr	Ser	Thr	Ser	Gly	Asp	Ser	
	2285						2290					2295				
	gcg	tcc	acc	cgc	agt	ctg	tcg	cgc	acc	gag	ggc	tcg	ctc	gcc	gag	6939
	Ala	Ser	Thr	Arg	Ser	Leu	Ser	Arg	Thr	Glu	Gly	Ser	Leu	Ala	Glu	
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	Asp	Glu	Pro	Pro	Gly	Pro	Ser	Gln	Ser	Ser	Arg	Arg	Leu	Pro	Arg	
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	2330						2335									

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Gly Gly Pro Trp His Glu Gln Val Glu Ile Thr Asp Glu Ser Thr Val
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Val Leu Asp Tyr Gln Asp His Lys Glu Ala Asp Ser His Ala Gly Val
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Lys Lys Phe Arg Cys Ile Glu Asn Leu Glu Lys Cys Val Lys Leu Glu
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Lys Ile Glu Gly Ile Glu Asn Leu Tyr Asn Leu Gln Lys Leu Asn Leu
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10	Gln	Asp	Val	Ser	Lys	Leu	Lys	Pro	Leu	Gln	Asp	Leu	Thr	Ser	Leu	Ile	
		210					215					220					
15	Leu	Leu	Glu	Asn	Pro	Val	Ala	Thr	Leu	Pro	His	Tyr	Ile	Gln	Phe	Thr	
	225					230					235					240	
20	Ile	Phe	His	Leu	Arg	Ser	Leu	Glu	Ser	Leu	Glu	Gly	Gln	Pro	Val	Thr	
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25	Ser	Gln	Asp	Arg	Gln	Glu	Ala	Phe	Ala	Arg	Phe	Ser	Leu	Asp	Glu	Val	
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30	Glu	Arg	Leu	Glu	Arg	Asp	Leu	Glu	Lys	Lys	Thr	Met	Glu	Thr	Glu	Glu	
			275					280					285				
35	Leu	Arg	Ser	Glu	Gln	Thr	Arg	Phe	Leu	Glu	Glu	Ile	Lys	Ser	Gln	Asp	
	290						295					300					
40	Lys	Leu	Asn	Lys	Ser	Leu	Lys	Glu	Glu	Ala	Arg	Leu	Gln	Lys	Gln	Ser	
	305					310					315					320	
45	Tyr	Glu	Glu	Leu	Glu	Ser	Asn	Leu	Asn	Thr	Lys	Asn	Glu	Leu	Leu	Lys	
				325						330					335		
50	Gln	Lys	Thr	Met	Glu	Leu	Met	Arg	Ala	Cys	Gln	Lys	Gln	Tyr	Glu	Met	
			340						345					350			
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	370						375					380					
65	Ser	Pro	Tyr	Ile	Gly	Lys	Ser	Arg	Tyr	Lys	Arg	Asn	Met	Phe	Thr	Thr	
	385					390					395					400	
70	Glu	Ser	Tyr	Ile	Ile	Ala	Asn	Ala	Gln	Thr	Val	Lys	Ile	Lys	Lys	Met	
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75	Glu	Leu	Asp	Glu	Gly	Glu	Gln	Leu	Arg	Asn	Glu	His	Val	Asn	Leu	Gly	
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5	Ala	Ala	Gln	Thr	Arg	Leu	Ser	Glu	Leu	His	Asp	Glu	Ile	Glu	Lys	Ala	
		450					455					460					
10	Glu	Gln	Gln	Ile	Leu	Arg	Ala	Thr	Glu	Glu	Phe	Lys	Gln	Leu	Glu	Glu	
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15	Ala	Ile	Gln	Leu	Lys	Lys	Ile	Ser	Glu	Ala	Glu	Lys	Asp	Leu	Leu	Phe	
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25	Ala	Val	Asp	Leu	Glu	Thr	Gln	Met	Glu	Lys	Gln	Arg	Gln	Glu	Ile	Gly	
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30	Glu	Lys	Gln	Asn	Glu	Ile	Lys	Asp	Leu	Glu	Ile	Val	Thr	Asp	Ser	Leu	
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35	Asp	Ser	Arg	Asp	Pro	Lys	His	Cys	His	Met	Lys	Ala	Gln	Lys	Arg	Gly	
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45	Ser	Arg	Leu	Asp	Glu	Ile	Leu	Ser	Arg	Ile	Ala	Lys	Glu	Thr	Glu	Glu	
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50	Ile	Lys	Asp	Leu	Glu	Glu	Gln	Leu	Thr	Glu	Gly	Gln	Ile	Ala	Ala	Asn	
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	625					630					635					640	
65	Arg	Lys	Leu	Gln	Asp	Glu	Lys	Glu	Thr	Leu	Leu	Gln	Arg	Leu	Ser	Glu	
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70	Val	Glu	Gln	Glu	Arg	Asp	Gln	Leu	Glu	Ile	Val	Ala	Ile	Asp	Ala	Glu	
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	675					680					685					
5	His	Glu	Val	Asn	Ile	Ser	Leu	Gln	Gln	Thr	Gln	Gly	Asp	Leu	Ser	Ala
	690						695					700				
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	705					710					715					720
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	770						775					780				
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10	Tyr	Ser	Pro	Ile	Arg	Ser	Gly	Leu	His	Lys	Ser	Phe	Ser	Asn	Arg
	1205						1210					1215			
15	Asp	Ala	Asp	Ser	Gly	Gly	Asp	Ser	Gln	Glu	Glu	Ser	Glu	Leu	Asp
	1220						1225					1230			
20	Asp	Gln	Glu	Asp	His	Pro	Phe	Val	Pro	Pro	Pro	Gly	Tyr	Met	Met
	1235						1240					1245			
25	Tyr	Thr	Val	Phe	Pro	Asp	Gly	Ser	Pro	Val	Pro	Gln	Gly	Met	Ala
	1250						1255					1260			
30	Leu	Tyr	Ala	Pro	Pro	Pro	Pro	Leu	Pro	Asn	Asn	Ser	Gln	Pro	Leu
	1265						1270					1275			
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	1280						1285					1290			
40	Ile	Val	Tyr	Gly	Pro	Pro	Pro	Pro	Asn	Phe	Ser	Val	Pro	Leu	Ile
	1295						1300					1305			
45	Pro	Val	Gly	Val	Leu	His	Cys	Asn	Val	Pro	Glu	His	His	Asn	Leu
	1310						1315					1320			
50	Glu	Asn	Glu	Val	Ser	Arg	Leu	Glu	Asp	Ile	Met	Gln	His	Leu	Lys
	1325						1330					1335			
55	Ser	Gly	Lys	Arg	Glu	Gln	Cys	Met	Lys	Thr	Pro	Lys	Leu	Gln	Ser
	1340						1345					1350			
60	Glu	Lys	Glu	Leu	Ala	Glu	Leu	Gln	His	Asn	Ile	Asp	Gly	Leu	Leu
	1355						1360					1365			
65	Gln	Glu	Lys	Lys	Asp	Leu	Glu	His	Glu	Val	Glu	Glu	Leu	His	Arg
	1370						1375					1380			
70	Thr	Ile	Gln	Lys	His	Gln	Gln	Arg	Lys	Asp	Phe	Ile	Asp	Gly	Asn
	1385						1390					1395			
75	Val	Glu	Ser	Leu	Val	Asn	Asp	Leu	Glu	Ile	Glu	Lys	Ser	Leu	Lys
	1400						1405					1410			

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	His His	Glu Asp Ile Val	Asp	Glu Ile Glu Cys Ile	Glu Arg Thr
	1415		1420	1425	
5	Leu Leu	Lys Arg Arg Ala	Glu	Leu Arg Glu Ala Asp	Arg Leu Leu
	1430		1435	1440	
10	Thr Glu	Ala Glu Ser Glu	Leu	Ser Cys Thr Lys Glu	Lys Thr Lys
	1445		1450	1455	
15	His Ala	Val Glu Lys Phe Thr	Asp Ala Lys Arg Asn	Leu Leu Gln	
	1460		1465	1470	
20	Thr Glu	Lys Asp Ala Glu Glu	Leu Glu Arg Arg Ala	Gln Glu Thr	
	1475		1480	1485	
25	Ala Ile	Asn Leu Val Lys Ala	Asp Gln Gln Leu Arg	Leu Leu Gln	
	1490		1495	1500	
30	Ala Asp	Thr Lys Asp Leu Glu	Gln His Lys Met Glu	Gln Glu Glu	
	1505		1510	1515	
35	Ile Leu	Lys Glu Ile Asn Lys	Val Val Ala Ala Lys	Asp Ser Asp	
	1520		1525	1530	
40	Phe Gln	Ser Leu Asn Lys Lys	Lys Glu Val Leu Thr	Gly Glu Leu	
	1535		1540	1545	
45	Gln Lys	Leu Gln Lys Asp Ile	Glu Thr Ala Arg His	Asn Glu Asp	
	1550		1555	1560	
50	Gln His	Leu Gln Val Leu Lys	Glu Ser Glu Thr Leu	Leu Gln Ala	
	1565		1570	1575	
55	Lys Lys	Ala Glu Leu Glu Asn	Leu Lys Ser Gln Val	Ser Gly Gln	
	1580		1585	1590	
60	Gln Gln	Glu Met Ala Val Leu	Asp Arg Glu Leu Gly	His Lys Lys	
	1595		1600	1605	
65	Glu Glu	Leu His Leu Leu Gln	Glu Ser Met Val Gln	Ala Lys Ala	
	1610		1615	1620	
70	Asp Leu	Gln Glu Ala Leu Arg	Leu Gly Glu Ser Glu	Val Thr Glu	
	1625		1630	1635	
75	Lys Cys	Asn His Ile Arg Glu	Val Lys Ser Leu Leu	Glu Glu Leu	

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	1640		1645		1650	
5	Ser Phe 1655	Gln Lys Gly Glu	Leu 1660	Asn Val Gln Ile	Ser 1665	Glu Lys Lys
10	Thr Gln 1670	Leu Ala Leu Ile	Lys 1675	Gln Glu Ile Glu	Lys 1680	Glu Glu Asp
15	Asn Leu 1685	Gln Val Val Leu	Gly 1690	Gln Met Ser Lys	His 1695	Lys Thr Glu
20	Leu Lys 1700	Asn Ile Leu Asp	Met 1705	Leu Gln Leu Glu	Asn 1710	Asn Glu Leu
25	Gln Gly 1715	Leu Lys Leu Gln	His 1720	Asp Gln Lys Met	Ser 1725	Glu Leu Glu
30	Lys Thr 1730	Arg Val Glu Val	Leu 1735	Glu Glu Lys Leu	Glu 1740	Leu Glu Ser
35	Leu Gln 1745	Gln Ala Ala Leu	Arg 1750	Gln Arg Gly Glu	Ile 1755	Glu Trp Gln
40	Lys Gln 1760	Leu Leu Gln Arg	Asn 1765	Thr Gln Glu Val	Glu 1770	Arg Met Thr
45	Ala Glu 1775	Thr Arg Ala Leu	Gln 1780	Ser Cys Val Glu	Ser 1785	Leu Cys Lys
50	Glu Lys 1790	Gln Asp Leu Glu	Glu 1795	Lys Gln Asp Ser	Trp 1800	Glu Lys Lys
55	Leu Ala 1805	Gln Thr Lys Arg	Val 1810	Leu Ala Ala Ala	Glu 1815	Glu Asp Ser
	Glu Met 1820	Glu Arg Ala Arg	Leu 1825	Glu Lys Leu Glu	Leu 1830	Asp Ala Arg
	Lys Leu 1835	Gln Gln Glu Leu	Asp 1840	Gln Arg Asn Arg	Glu 1845	Lys Leu Ser
	Leu His 1850	Gln Asp Leu Ala	Val 1855	Val Gln Gln Gln	Leu 1860	Gln Glu Lys
	Gln Glu 1865	Ala Val Asn Ser	Leu 1870	Gln Lys Glu Leu	Thr 1875	Asp Val Gln

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	Glu 1880	His	Leu	Asp	Leu	Ala	Glu 1885	Gln	Glu	Val	Leu	Cys 1890	Thr	Thr	Lys
5	Arg 1895	Lys	Asp	Ala	Leu	Leu	Ser 1900	Glu	Gln	Thr	Arg	Leu 1905	Glu	Lys	Asp
10	Val 1910	Gly	Glu	Trp	Thr	Lys	Lys 1915	Phe	Glu	Asp	Cys	Gln 1920	Lys	Glu	Gly
	Glu 1925	Thr	Lys	Gln	Gln	Gln	Leu 1930	Gln	Gly	Leu	Gln	Lys 1935	Glu	Ile	Glu
15	Gly 1940	Asn	Glu	Ala	Lys	Leu	Ala 1945	Gln	Gln	Glu	Met	Met 1950	Phe	Gln	Arg
20	Leu 1955	Gln	Lys	Glu	Arg	Glu	Cys 1960	Glu	Glu	Lys	Lys	Leu 1965	Glu	Ala	Ser
	Lys 1970	Val	Thr	Leu	Lys	Glu	Gln 1975	Gln	Gln	Gln	Leu	Glu 1980	Lys	Glu	Leu
25	Met 1985	Glu	Gln	Lys	Gly	Lys	Leu 1990	Asp	Gln	Val	Leu	Ala 1995	Lys	Leu	Leu
30	Val 2000	Ala	Glu	Glu	Arg	Val	Arg 2005	Thr	Leu	Gln	Glu	Glu 2010	Gly	Arg	Trp
	Ser 2015	Glu	Thr	Leu	Glu	Lys	Thr 2020	Leu	Ser	Gln	Thr	Lys 2025	Arg	Gln	Leu
35	Ser 2030	Glu	Arg	Glu	Gln	Gln	Leu 2035	Leu	Ala	Lys	Ser	Asp 2040	Glu	Leu	Leu
40	Ala 2045	Leu	Gln	Lys	Glu	Thr	Asp 2050	Ser	Met	Arg	Ala	Asp 2055	Phe	Ser	Leu
45	Leu 2060	Arg	Asn	Gln	Phe	Leu	Thr 2065	Glu	Arg	Lys	Lys	Ala 2070	Glu	Lys	Gln
	Val 2075	Ala	Ser	Leu	Lys	Glu	Ala 2080	Leu	Lys	Ile	Gln	Arg 2085	Ser	Gln	Leu
50	Glu 2090	Lys	Asn	Leu	Leu	Glu	Gln 2095	Lys	Gln	Glu	Asn	Ser 2100	Cys	Met	Gln
55	Arg 2105	Glu	Met	Ala	Thr	Ile	Glu 2110	Gln	Val	Ala	Gln	Asp 2115	Asn	His	Glu

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5	Tyr	Val	Glu	Leu	Arg	Lys	Gln	Met	Thr	Asn	Gln	Lys	Asp	Leu	Glu
	2135						2140					2145			
10	Arg	Arg	Gln	Met	Glu	Ile	Ser	Asp	Ala	Met	Gln	Ala	Leu	Lys	Cys
	2150						2155					2160			
15	Glu	Val	Lys	Asp	Glu	Ile	Arg	Thr	Ser	Leu	Lys	Asn	Leu	Asn	Gln
	2165						2170					2175			
20	Phe	Leu	Pro	Glu	Leu	Pro	Ala	Asp	Leu	Glu	Ala	Leu	Leu	Glu	Arg
	2180						2185					2190			
25	Asn	Glu	Asn	Leu	Gly	Gly	Gly	Leu	Glu	Ser	Leu	Lys	Glu	Asn	Phe
	2195						2200					2205			
30	Pro	Phe	Thr	Val	Ser	Asp	Arg	Pro	Ser	Ser	Cys	Glu	Glu	Lys	Leu
	2210						2215					2220			
35	Asn	Phe	Gly	Gln	Ala	His	Val	Ala	Asp	Glu	Gln	Trp	Arg	Gly	Glu
	2225						2230					2235			
40	Ala	Leu	Arg	Glu	Lys	Leu	Arg	His	Arg	Glu	Asp	Arg	Leu	Lys	Ala
	2240						2245					2250			
45	Gln	Leu	Arg	Arg	Cys	Met	Ser	Lys	Gln	Ala	Glu	Val	Leu	Ser	Glu
	2255						2260					2265			
50	Gly	Arg	Arg	Arg	Thr	Glu	Gly	Thr	Leu	His	Ser	Leu	Arg	Arg	Gln
	2270						2275					2280			
55	Val	Asp	Ala	Leu	Gly	Glu	Leu	Val	Thr	Ser	Thr	Ser	Gly	Asp	Ser
	2285						2290					2295			
60	Ala	Ser	Thr	Arg	Ser	Leu	Ser	Arg	Thr	Glu	Gly	Ser	Leu	Ala	Glu
	2300						2305					2310			
65	Asp	Glu	Pro	Pro	Gly	Pro	Ser	Gln	Ser	Ser	Arg	Arg	Leu	Pro	Arg
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70	Gly	Pro	Ser	Pro	Arg	Leu	Asp	Ala	His	Arg	Pro				
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<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(7770)
<223>

<400> 27

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	1 5 10 15	
	tca tct cac tct cct agt cca cca tcc ctt acg tcc aat atg aga tct	96
15	Ser Ser His Ser Pro Ser Pro Pro Ser Leu Thr Ser Asn Met Arg Ser	
	20 25 30	
	agg tca ctt tcg cct cta agt gga tct gag act ctg cct ttt cat ttt	144
	Arg Ser Leu Ser Pro Leu Ser Gly Ser Glu Thr Leu Pro Phe His Phe	
	35 40 45	
20	gga gga ccg tgg cat gag caa gtt gag att aca gat gaa agc aca gtg	192
	Gly Gly Pro Trp His Glu Gln Val Glu Ile Thr Asp Glu Ser Thr Val	
	50 55 60	
	gtt tta gac tac caa gac cat aaa gaa gct gat tca cat gca gga gtc	240
25	Val Leu Asp Tyr Gln Asp His Lys Glu Ala Asp Ser His Ala Gly Val	
	65 70 75 80	
	cga tat att aca gag gcc ctt gtt aga aaa ctt act aaa cag gac aat	288
	Arg Tyr Ile Thr Glu Ala Leu Val Arg Lys Leu Thr Lys Gln Asp Asn	
	85 90 95	
30	ttg gcc ttg gta aaa tct ctg aac ctt tca ctt gct aaa ggt ggt ggc	336
	Leu Ala Leu Val Lys Ser Leu Asn Leu Ser Leu Ala Lys Gly Gly Gly	
	100 105 110	
	aag aaa ttc agg tgt atc gaa aat ttg gaa aaa tgt gtt aaa ctt gaa	384
35	Lys Lys Phe Arg Cys Ile Glu Asn Leu Glu Lys Cys Val Lys Leu Glu	
	115 120 125	
	gta ctg aat ctc agc tat aat cta ata gga aag att gag aaa gtg gac	432
	Val Leu Asn Leu Ser Tyr Asn Leu Ile Gly Lys Ile Glu Lys Val Asp	
	130 135 140	
40	aaa ctg tta aaa tta cgt gaa ctc aac tta tcg tat aac aaa atc cgc	480
	Lys Leu Leu Lys Leu Arg Glu Leu Asn Leu Ser Tyr Asn Lys Ile Arg	
	145 150 155 160	
	aaa att gaa ggc ata gaa aat tta tat aat ctg caa aag ctg aac ctt	528
45	Lys Ile Glu Gly Ile Glu Asn Leu Tyr Asn Leu Gln Lys Leu Asn Leu	
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	gca gga aat gaa atc gaa cat atc cca gta tgg tta ggg aag aag tta	576
50	Ala Gly Asn Glu Ile Glu His Ile Pro Val Trp Leu Gly Lys Lys Leu	
	180 185 190	
	aaa tct ttg cga atc ctg aat ctg aaa ggc aac aag ata tca tcg ctc	624
	Lys Ser Leu Arg Ile Leu Asn Leu Lys Gly Asn Lys Ile Ser Ser Leu	
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55	caa gat gta agc aag ttg aaa cca ctt caa gat ttg act tct ctg atc	672
	Gln Asp Val Ser Lys Leu Lys Pro Leu Gln Asp Leu Thr Ser Leu Ile	

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5	cta ctt gaa aat cca gtt gcg acc ctt cct cat tat atc cag ttt acc Leu Leu Glu Asn Pro Val Ala Thr Leu Pro His Tyr Ile Gln Phe Thr 225 230 235 240	720		
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15	agt cag gac aga caa gaa gct ttt gcg aga ttc agt tta gat gag gta Ser Gln Asp Arg Gln Glu Ala Phe Ala Arg Phe Ser Leu Asp Glu Val 260 265 270	816		
20	gaa aga ctg gaa aga gac ctg gag aag aag aca atg gaa act gaa gag Glu Arg Leu Glu Arg Asp Leu Glu Lys Lys Thr Met Glu Thr Glu Glu 275 280 285	864		
25	ctt agg agt gag cag aca agg ttc ctt gag gaa att aaa agt cag gat Leu Arg Ser Glu Gln Thr Arg Phe Leu Glu Glu Ile Lys Ser Gln Asp 290 295 300	912		
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55	agc cct tac att ggc aaa tcc aga tac aag aga aat atg ttc act aca Ser Pro Tyr Ile Gly Lys Ser Arg Tyr Lys Arg Asn Met Phe Thr Thr 385 390 395 400	1200		
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65	gag cta gat gaa ggg gaa caa ctc aga aat gag cac gtg aac ttg gga Glu Leu Asp Glu Gly Glu Gln Leu Arg Asn Glu His Val Asn Leu Gly 420 425 430	1296		
70	gca tcg cca aca gac ata caa ctg gaa gac aaa gaa aaa aaa ata agt Ala Ser Pro Thr Asp Ile Gln Leu Glu Asp Lys Glu Lys Lys Ile Ser 435 440 445	1344		
75	gca gca caa act cga cta tca gaa cta cat gat gaa ata gaa aag gca Ala Ala Gln Thr Arg Leu Ser Glu Leu His Asp Glu Ile Glu Lys Ala 450 455 460	1392		
80	gaa caa caa att tta aga gcc act gaa gaa ttt aaa caa ctg gaa gaa	1440		

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	Glu 465	Gln	Gln	Ile	Leu	Arg 470	Ala	Thr	Glu	Glu	Phe 475	Lys	Gln	Leu	Glu	Glu 480	
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10	aag Lys	cag Gln	ttg Leu	agt Ser	ggt Gly	agg Arg	ata Ile	cag Gln	ctt Leu	ctc Leu	aat Asn	aaa Lys	tta Leu	cgc Arg	caa Gln	gaa Glu	1536
15	gct Ala	gtg Val	gat Asp	cta Leu	gaa Glu	aca Thr	cag Gln	atg Met	gaa Glu	aag Lys	caa Gln	agg Arg	caa Gln	gaa Glu	att Ile	ggt Gly	1584
20	gaa Glu	aag Lys	cag Gln	aat Asn	gag Glu	atc Ile	aag Lys	gac Asp	ctg Leu	gaa Glu	ata Ile	gtc Val	aca Thr	gat Asp	agc Ser	ctg Leu	1632
25	gat Asp	tcc Ser	aga Arg	gac Asp	cca Pro	aaa Lys	cat His	tgc Cys	cat His	atg Met	aag Lys	gct Ala	cag Gln	aaa Lys	aga Arg	ggt Gly	1680
30	aaa Lys	gaa Glu	caa Gln	caa Gln	ctt Leu	gac Asp	att Ile	atg Met	aac Asn	aag Lys	cag Gln	tac Tyr	aaa Lys	cag Gln	ctt Leu	gaa Glu	1728
35	agc Ser	cgt Arg	ttg Leu	gat Asp	gag Glu	ata Ile	ctt Leu	tct Ser	aga Arg	att Ile	gcc Ala	aaa Lys	gaa Glu	act Thr	gaa Glu	gag Glu	1776
40	att Ile	aag Lys	gac Asp	ctt Leu	gaa Glu	gaa Glu	cag Gln	ctt Leu	act Thr	gaa Glu	gga Gly	caa Gln	ata Ile	gcc Ala	gca Ala	aac Asn	1824
45	gaa Glu	gcc Ala	ctg Leu	aag Lys	aag Lys	gac Asp	tta Leu	gaa Glu	agt Ser	gtc Val	atc Ile	agt Ser	ggg Gly	ttg Leu	caa Gln	gaa Glu	1872
50	tac Tyr	ctg Leu	gag Glu	act Thr	gtc Val	aaa Gly	ggt Gln	cag Gln	gcc Ala	cgt Arg	cag Gln	gcc Ala	cag Gln	aat Asn	gag Glu	tgc Cys	1920
55	aga Arg	aag Lys	cta Leu	cag Gln	gat Asp	gag Glu	aag Lys	gag Glu	aca Thr	ttg Leu	ctg Leu	cag Gln	aga Arg	ttg Leu	agt Ser	gag Glu	1968
60	gtc Val	gag Glu	cag Gln	gag Glu	agg Arg	gac Asp	caa Gln	ctg Leu	gaa Glu	ata Ile	gtg Val	gcc Ala	ata Ile	gat Asp	gca Ala	gaa Glu	2016
65	aat Asn	atg Met	agg Arg	aag Lys	gag Glu	ctc Leu	gca Ala	gaa Glu	ctg Leu	gag Glu	aat Asn	gcc Ala	ctc Leu	cag Gln	gag Glu	cag Gln	2064
70	cat His	gag Glu	gtg Val	aat Asn	ata Ile	tct Ser	ctg Leu	cag Gln	cag Gln	acc Thr	cag Gln	gga Gly	gat Asp	ctc Leu	agt Ser	gcc Ala	2112
75	tat Tyr	gag Glu	gct Ala	gag Glu	cta Leu	gag Glu	gct Ala	cag Gln	ctg Leu	aaa Lys	ata Ile	cgg Arg	gat Asp	gct Ala	gaa Glu	gcc Ala	2160

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	aac cag ctc aag gag gag ttg gaa aaa ctt aga agg ttg agc cag tta	2208
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5	gaa caa tcg gcc ctt caa gca gag ctt gag aag gaa aag caa gcc ttc	2256
	Glu Gln Ser Ala Leu Gln Ala Glu Leu Glu Lys Glu Lys Gln Ala Phe	
	740 745 750	
10	aag act gct gtc aaa aaa gcc cag ctc tca gaa gga aag gac caa gaa	2304
	Lys Thr Ala Val Lys Lys Ala Gln Leu Ser Glu Gly Lys Asp Gln Glu	
	755 760 765	
15	aat agt gag ctc cgc aca caa ctc caa cag ctg cag gat gac aat gac	2352
	Asn Ser Glu Leu Arg Thr Gln Leu Gln Gln Leu Gln Asp Asp Asn Asp	
	770 775 780	
20	cta ttg aaa cag caa ctt aaa gat ttc cag agt cac ctt aac cat gtg	2400
	Leu Leu Lys Gln Gln Leu Lys Asp Phe Gln Ser His Leu Asn His Val	
	785 790 795 800	
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	Val Asp Gly Leu Ile Arg Pro Glu Glu Val Ala Ala Cys Val Asp Glu	
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30	cta agg aaa aaa ctg aag tca gga gct ggg gaa atg aga atc cat act	2496
	Leu Arg Lys Lys Leu Lys Ser Gly Ala Gly Glu Met Arg Ile His Thr	
	820 825 830	
35	cct tca gat gtc tta ggg aaa agt ctt gct gac ttg cag aag caa ttc	2544
	Pro Ser Asp Val Leu Gly Lys Ser Leu Ala Asp Leu Gln Lys Gln Phe	
	835 840 845	
40	agt gag atc ctg gca cgc tcc cag tgg gaa aga cag gaa gca caa gtg	2592
	Ser Glu Ile Leu Ala Arg Ser Gln Trp Glu Arg Gln Glu Ala Gln Val	
	850 855 860	
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	Arg Glu Arg Lys Leu Gln Glu Glu Met Ala Leu Gln Gln Glu Lys Leu	
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	Ala Ser Gly Gln Glu Glu Phe Arg His Ala Cys Glu Arg Ala Leu Glu	
	885 890 895	
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	Ala Arg Ile Ser Phe Asp Lys Arg Gln His Glu Ala Arg Ile Gln Gln	
	900 905 910	
60	ttg gag aat gaa att cac tat ttg caa gaa aat cta aaa agt atg gag	2784
	Leu Glu Asn Glu Ile His Tyr Leu Gln Glu Asn Leu Lys Ser Met Glu	
	915 920 925	
65	gaa atc caa ggt ctc aca gac ctc caa ctt cag gaa gct gat gaa gag	2832
	Glu Ile Gln Gly Leu Thr Asp Leu Gln Leu Gln Glu Ala Asp Glu Glu	
	930 935 940	
70	aag gag aga att ctg gcc caa ctc cgg gag tta gag aaa aag aag aaa	2880
	Lys Glu Arg Ile Leu Ala Gln Leu Arg Glu Leu Glu Lys Lys Lys Lys	
	945 950 955 960	
75	ctt gag gat gcc aag tct cag gag cag ttt ctt gga tta gat aga gaa	2928
	Leu Glu Asp Ala Lys Ser Gln Glu Gln Phe Leu Gly Leu Asp Arg Glu	
	965 970 975	

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	ttg aag aag cta aag aaa gct gtg gct gcc tct gat aag ctg gcc aca	2976
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5	gct gag ctc acc att gcc aaa gac cag ctc aag tcc ctt cat gga act	3024
	Ala Glu Leu Thr Ile Ala Lys Asp Gln Leu Lys Ser Leu His Gly Thr	
	995 1000 1005	
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	Val Met Lys Ile Asn Gln Glu Arg Ala Glu Glu Leu Gln Glu Thr	
	1010 1015 1020	
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	Lys Glu Glu Gln Phe Arg Asn Glu Ile Glu Lys Val Asp Val Gly	
	1055 1060 1065	
30	tct gga gga gca aag tca cag atg ctg gag atg gag aaa cta aat	3249
	Ser Gly Gly Ala Lys Ser Gln Met Leu Glu Met Glu Lys Leu Asn	
	1070 1075 1080	
35	gag aca atg gag agg caa aga aca gag att gct agg ctg agg aat	3294
	Glu Thr Met Glu Arg Gln Arg Thr Glu Ile Ala Arg Leu Arg Asn	
	1085 1090 1095	
40	tta cta gac ctc acc ggg gct gat aac aaa gga aac ttt gaa aat	3339
	Leu Leu Asp Leu Thr Gly Ala Asp Asn Lys Gly Asn Phe Glu Asn	
	1100 1105 1110	
45	gtt ttg gaa gaa att gct gaa ctt cga cgt gaa gtt tct cat cag	3384
	Val Leu Glu Glu Ile Ala Glu Leu Arg Arg Glu Val Ser His Gln	
	1115 1120 1125	
50	aat gat tac atc agc agc atg aca gat cct ttc aaa aga cga ggc	3429
	Asn Asp Tyr Ile Ser Ser Met Thr Asp Pro Phe Lys Arg Arg Gly	
	1130 1135 1140	
55	tat tgg tac ttt atg cca cca cca tca tca tca aaa gtt tcc agc	3474
	Tyr Trp Tyr Phe Met Pro Pro Pro Ser Ser Ser Lys Val Ser Ser	
	1145 1150 1155	
60	cac agt tcc cag gcc acc aag gac tct ggt gtt ggc cta aag tac	3519
	His Ser Ser Gln Ala Thr Lys Asp Ser Gly Val Gly Leu Lys Tyr	
	1160 1165 1170	
65	aca gcc tcc act ccg gtt aga aaa cca cat cgt gga cgg cag gat	3564
	Thr Ala Ser Thr Pro Val Arg Lys Pro His Arg Gly Arg Gln Asp	
	1175 1180 1185	
70	gga aag gag aac agt ggg cct cca cct gcc tca gga tac tgg gtg	3609
	Gly Lys Glu Asn Ser Gly Pro Pro Pro Ala Ser Gly Tyr Trp Val	
	1190 1195 1200	
75	tat tct cct atc agg agt ggg tta cat aaa tcg ttc tca aat aga	3654
	Tyr Ser Pro Ile Arg Ser Gly Leu His Lys Ser Phe Ser Asn Arg	

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	1205	1210	1215	
5	gac gca gac agt gga gga gat Asp Ala Asp Ser Gly Gly Asp 1220	agc cag gaa gag agc Ser Gln Glu Glu Ser 1225	gag cta gat Glu Leu Asp 1230	3699
	gac caa gaa gac cac cca ttt Asp Gln Glu Asp His Pro Phe 1235	gta cct cct cct gga Val Pro Pro Pro Gly 1240	tac atg atg Tyr Met Met 1245	3744
10	tac act gtg ttt cct gat ggt Tyr Thr Val Phe Pro Asp Gly 1250	tct cct gta ccc cag Ser Pro Val Pro Gln 1255	ggc atg gcc Gly Met Ala 1260	3789
15	ctg tat gca ccc cct cct ccc Leu Tyr Ala Pro Pro Pro 1265	ttg ccc aac aat agc Leu Pro Asn Asn Ser 1270	cag cct ctt Gln Pro Leu 1275	3834
20	gac ctt ggc act gtt gtt tat Asp Leu Gly Thr Val Val Tyr 1280	ggc cca cct cct gtt Gly Pro Pro Pro Val 1285	ggg gct ccc Gly Ala Pro 1290	3879
	atc gtg tat ggg cct cca cct Ile Val Tyr Gly Pro Pro Pro 1295	ccc aac ttc tcc gta Pro Asn Phe Ser Val 1300	ccc ctc atc Pro Leu Ile 1305	3924
25	ccc gtg ggt gtg ctg cac tgc Pro Val Gly Val Leu His Cys 1310	aat gtc cca gaa cac Asn Val Pro Glu His 1315	cat aac ttg His Asn Leu 1320	3969
30	gag aat gaa gtt tct aga tta Glu Asn Glu Val Ser Arg Leu 1325	gaa gac ata atg cag Glu Asp Ile Met Gln 1330	cat tta aaa His Leu Lys 1335	4014
	tct ggg aaa cgg gaa cag tgc Ser Gly Lys Arg Glu Gln Cys 1340	atg aaa aca ccc aag Met Lys Thr Pro Lys 1345	ctg cag tcg Leu Gln Ser 1350	4059
35	gag aaa gaa ctc gca gag ctg Glu Lys Glu Leu Ala Glu Leu 1355	cag cat aac att gat Gln His Asn Ile Asp 1360	ggt ctt ttg Gly Leu Leu 1365	4104
40	caa gag aag aaa gac tta gag Gln Glu Lys Lys Asp Leu Glu 1370	cat gaa gta gaa gaa His Glu Val Glu Glu 1375	tta cat aga Leu His Arg 1380	4149
	acc atc caa aaa cat caa cag Thr Ile Gln Lys His Gln Gln 1385	cga aaa gat ttc att Arg Lys Asp Phe Ile 1390	gat gga aac Asp Gly Asn 1395	4194
45	gtt gag agt ctt gtg aat gat Val Glu Ser Leu Val Asn Asp 1400	cta gaa ata gag aag Leu Glu Ile Glu Lys 1405	tca ctc aaa Ser Leu Lys 1410	4239
50	cac cat gaa gat att gtt gat His His Glu Asp Ile Val Asp 1415	gaa att gaa tgt att Glu Ile Glu Cys Ile 1420	gag agg acc Glu Arg Thr 1425	4284
	ctt ctg aag cgc cgt gca gag Leu Leu Lys Arg Arg Ala Glu 1430	ctc agg gaa gcc gac Leu Arg Glu Ala Asp 1435	cgg ctg ctg Arg Leu Leu 1440	4329
55	acg gag gct gaa agt gaa ctt 1445	tca tgc acg aaa gag 1450	aaa aca aaa 1455	4374

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	Thr	Glu	Ala	Glu	Ser	Glu	Leu	Ser	Cys	Thr	Lys	Glu	Lys	Thr	Lys	
	1445						1450					1455				
5	cat	gct	gtt	gag	aag	ttc	act	gat	gcc	aag	aga	aat	tta	ttg	caa	4419
	His	Ala	Val	Glu	Lys	Phe	Thr	Asp	Ala	Lys	Arg	Asn	Leu	Leu	Gln	
	1460						1465					1470				
10	act	gag	aaa	gat	gct	gag	gag	tta	gaa	agg	aga	gcc	cag	gaa	act	4464
	Thr	Glu	Lys	Asp	Ala	Glu	Glu	Leu	Glu	Arg	Arg	Ala	Gln	Glu	Thr	
	1475						1480					1485				
	gcc	att	aac	ctc	gtc	aaa	gcc	gac	cag	cag	ctg	aga	ttg	ctc	cag	4509
	Ala	Ile	Asn	Leu	Val	Lys	Ala	Asp	Gln	Gln	Leu	Arg	Leu	Leu	Gln	
	1490						1495					1500				
15	gct	gac	acg	aag	gat	ttg	gag	cag	cac	aaa	atg	gag	caa	gag	gaa	4554
	Ala	Asp	Thr	Lys	Asp	Leu	Glu	Gln	His	Lys	Met	Glu	Gln	Glu	Glu	
	1505						1510					1515				
20	atc	ttg	aaa	gaa	ata	aac	aaa	gtt	gtt	gca	gca	aaa	gac	tca	gac	4599
	Ile	Leu	Lys	Glu	Ile	Asn	Lys	Val	Val	Ala	Ala	Lys	Asp	Ser	Asp	
	1520						1525					1530				
25	ttc	cag	agc	cta	aac	aag	aag	aag	gaa	gta	ctg	aca	gga	gag	ctg	4644
	Phe	Gln	Ser	Leu	Asn	Lys	Lys	Lys	Glu	Val	Leu	Thr	Gly	Glu	Leu	
	1535						1540					1545				
	cag	aaa	ctc	cag	aag	gac	att	gag	act	gca	cgg	cac	aat	gag	gat	4689
	Gln	Lys	Leu	Gln	Lys	Asp	Ile	Glu	Thr	Ala	Arg	His	Asn	Glu	Asp	
	1550						1555					1560				
30	cag	cac	ctg	cag	gtc	ctt	aaa	gag	tcg	gag	acc	ctc	ctg	cag	gcc	4734
	Gln	His	Leu	Gln	Val	Leu	Lys	Glu	Ser	Glu	Thr	Leu	Leu	Gln	Ala	
	1565						1570					1575				
35	aag	aaa	gct	gag	ctg	gaa	aat	ctg	aaa	agc	cag	gtg	tca	gga	cag	4779
	Lys	Lys	Ala	Glu	Leu	Glu	Asn	Leu	Lys	Ser	Gln	Val	Ser	Gly	Gln	
	1580						1585					1590				
	cag	cag	gag	atg	gcc	gtc	ttg	gac	agg	gag	tta	gga	cac	aag	aag	4824
	Gln	Gln	Glu	Met	Ala	Val	Leu	Asp	Arg	Glu	Leu	Gly	His	Lys	Lys	
	1595						1600					1605				
40	gaa	gag	ctg	cat	ctc	ctc	cag	gaa	agc	atg	gtc	cag	gcc	aaa	gct	4869
	Glu	Glu	Leu	His	Leu	Leu	Gln	Glu	Ser	Met	Val	Gln	Ala	Lys	Ala	
	1610						1615					1620				
45	gac	ctc	cag	gaa	gca	ctg	aga	cta	gga	gaa	agt	gaa	gta	act	gag	4914
	Asp	Leu	Gln	Glu	Ala	Leu	Arg	Leu	Gly	Glu	Ser	Glu	Val	Thr	Glu	
	1625						1630					1635				
50	aag	tgc	aat	cac	att	agg	gaa	gta	aaa	tct	ctt	ctg	gaa	gaa	ctc	4959
	Lys	Cys	Asn	His	Ile	Arg	Glu	Val	Lys	Ser	Leu	Leu	Glu	Glu	Leu	
	1640						1645					1650				
	agt	ttt	cag	aaa	gga	gaa	ctg	aat	gtc	cag	atc	agt	gaa	aaa	aaa	5004
	Ser	Phe	Gln	Lys	Gly	Glu	Leu	Asn	Val	Gln	Ile	Ser	Glu	Lys	Lys	
	1655						1660					1665				
55	act	caa	ctt	gca	ctc	ata	aag	cag	gaa	att	gaa	aaa	gag	gaa	gac	5049
	Thr	Gln	Leu	Ala	Leu	Ile	Lys	Gln	Glu	Ile	Glu	Lys	Glu	Glu	Asp	
	1670						1675					1680				

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	aat ctt cag gta gtt tta ggg caa atg tct aaa cat aaa act gaa	5094
	Asn Leu Gln Val Val Leu Gly Gln Met Ser Lys His Lys Thr Glu	
	1685 1690 1695	
5	cta aag aat att ctg gac atg ttg caa ctt gaa aat aat gag ctg	5139
	Leu Lys Asn Ile Leu Asp Met Leu Gln Leu Glu Asn Asn Glu Leu	
	1700 1705 1710	
10	caa ggt ttg aag ctc caa cat gac caa aag atg tct gaa tta gag	5184
	Gln Gly Leu Lys Leu Gln His Asp Gln Lys Met Ser Glu Leu Glu	
	1715 1720 1725	
15	aag act cgg gtt gaa gtg ctg gag gag aaa ctg gag tta gag agt	5229
	Lys Thr Arg Val Glu Val Leu Glu Glu Lys Leu Glu Leu Glu Ser	
	1730 1735 1740	
20	ctg cag cag gca gcc ctg cga cag aga ggg gag ata gag tgg cag	5274
	Leu Gln Gln Ala Ala Leu Arg Gln Arg Gly Glu Ile Glu Trp Gln	
	1745 1750 1755	
25	aag cag ctc ctc cag agg aac aca cag gaa gta gag cgg atg act	5319
	Lys Gln Leu Leu Gln Arg Asn Thr Gln Glu Val Glu Arg Met Thr	
	1760 1765 1770	
30	gct gag acc cga gca tta cag tca tgt gtt gag tct ttg tgc aaa	5364
	Ala Glu Thr Arg Ala Leu Gln Ser Cys Val Glu Ser Leu Cys Lys	
	1775 1780 1785	
35	gaa aag caa gat ctc gaa gaa aaa cag gac agc tgg gaa aag aag	5409
	Glu Lys Gln Asp Leu Glu Glu Lys Gln Asp Ser Trp Glu Lys Lys	
	1790 1795 1800	
40	ttg gca cag acc aaa cgg gtt cta gca gct gca gaa gag gac agc	5454
	Leu Ala Gln Thr Lys Arg Val Leu Ala Ala Ala Glu Glu Asp Ser	
	1805 1810 1815	
45	gag atg gag cgg gca cgc tta gaa aag ttg gaa ctg gac gcc agg	5499
	Glu Met Glu Arg Ala Arg Leu Glu Lys Leu Glu Leu Asp Ala Arg	
	1820 1825 1830	
50	aag ctg cag cag gag ttg gac caa cga aac agg gag aag ctc tcc	5544
	Lys Leu Gln Gln Glu Leu Asp Gln Arg Asn Arg Glu Lys Leu Ser	
	1835 1840 1845	
55	ctg cat caa gac ctg gca gtg gtg cag cag cag cta caa gaa aaa	5589
	Leu His Gln Asp Leu Ala Val Val Gln Gln Gln Leu Gln Glu Lys	
	1850 1855 1860	
60	cag gaa gca gta aac tca tta cag aag gaa cta gct gat gtc cag	5634
	Gln Glu Ala Val Asn Ser Leu Gln Lys Glu Leu Ala Asp Val Gln	
	1865 1870 1875	
65	gag cat ttg gac cta gca gaa cag gag gtg ctc tgc acc acc aag	5679
	Glu His Leu Asp Leu Ala Glu Gln Glu Val Leu Cys Thr Thr Lys	
	1880 1885 1890	
70	cgc aag gac gca ctg ctc agc gaa cag acc agg ctc gag aag gac	5724
	Arg Lys Asp Ala Leu Leu Ser Glu Gln Thr Arg Leu Glu Lys Asp	
	1895 1900 1905	
75	gtg ggt gaa tgg acg aag aag ttt gaa gac tgc cag aaa gaa ggg	5769
	Val Gly Glu Trp Thr Lys Lys Phe Glu Asp Cys Gln Lys Glu Gly	
	1910 1915 1920	

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		gag	aca	aag	cag	caa	cag	ctt	caa	ggg	ctt	cag	aag	gag	att	gaa	5814
		Glu	Thr	Lys	Gln	Gln	Gln	Leu	Gln	Gly	Leu	Gln	Lys	Glu	Ile	Glu	
		1925						1930					1935				
5		gga	aac	gag	gcg	aag	cta	gcc	caa	caa	gaa	atg	atg	ttt	cag	aga	5859
		Gly	Asn	Glu	Ala	Lys	Leu	Ala	Gln	Gln	Glu	Met	Met	Phe	Gln	Arg	
		1940						1945					1950				
10		ctc	cag	aaa	gag	cga	gaa	tgt	gaa	gaa	aaa	aag	tta	gaa	gct	agt	5904
		Leu	Gln	Lys	Glu	Arg	Glu	Cys	Glu	Glu	Lys	Lys	Leu	Glu	Ala	Ser	
		1955						1960					1965				
15		aaa	gtg	act	ctg	aag	gag	cag	cag	caa	cag	ctg	gaa	aag	gaa	ttg	5949
		Lys	Val	Thr	Leu	Lys	Glu	Gln	Gln	Gln	Gln	Leu	Glu	Lys	Glu	Leu	
		1970						1975					1980				
20		atg	gag	cag	aaa	ggc	aag	ctg	gac	cag	gtg	ctc	gct	aag	ctc	ttg	5994
		Met	Glu	Gln	Lys	Gly	Lys	Leu	Asp	Gln	Val	Leu	Ala	Lys	Leu	Leu	
		1985						1990					1995				
25		gtg	gct	gag	gag	cgt	gtc	agg	acc	ttg	cag	gag	gag	gga	agg	tg	6039
		Val	Ala	Glu	Glu	Arg	Val	Arg	Thr	Leu	Gln	Glu	Glu	Gly	Arg	Trp	
		2000						2005					2010				
30		agc	gag	acc	ctg	gag	aag	acg	ctc	tcc	cag	acc	aag	cga	cag	ctt	6084
		Ser	Glu	Thr	Leu	Glu	Lys	Thr	Leu	Ser	Gln	Thr	Lys	Arg	Gln	Leu	
		2015						2020					2025				
35		tca	gaa	cgg	gag	cag	cag	tta	ctg	gcc	aag	tca	gac	gag	ctg	ctg	6129
		Ser	Glu	Arg	Glu	Gln	Gln	Leu	Leu	Ala	Lys	Ser	Asp	Glu	Leu	Leu	
		2030						2035					2040				
40		gcc	ctg	cag	aag	gag	acg	gac	tcc	atg	agg	gcg	gac	ttc	agc	ctc	6174
		Ala	Leu	Gln	Lys	Glu	Thr	Asp	Ser	Met	Arg	Ala	Asp	Phe	Ser	Leu	
		2045						2050					2055				
45		ttg	cgc	aac	cag	ttc	ctg	aca	gaa	aga	aag	aaa	gcc	gag	aag	cag	6219
		Leu	Arg	Asn	Gln	Phe	Leu	Thr	Glu	Arg	Lys	Lys	Ala	Glu	Lys	Gln	
		2060						2065					2070				
50		gtg	gcc	agc	ctg	aag	gaa	gcc	ctt	aag	atc	cag	cgg	agc	caa	ctg	6264
		Val	Ala	Ser	Leu	Lys	Glu	Ala	Leu	Lys	Ile	Gln	Arg	Ser	Gln	Leu	
		2075						2080					2085				
55		gag	aag	aac	ctt	ctg	gag	caa	aag	cag	gag	aac	agc	tgc	atg	cag	6309
		Glu	Lys	Asn	Leu	Leu	Glu	Gln	Lys	Gln	Glu	Asn	Ser	Cys	Met	Gln	
		2090						2095					2100				
60		agg	gag	atg	gca	acc	atc	gaa	cag	gtg	gcc	cag	gac	aac	cac	gag	6354
		Arg	Glu	Met	Ala	Thr	Ile	Glu	Gln	Val	Ala	Gln	Asp	Asn	His	Glu	
		2105						2110					2115				
65		cgg	gcc	cgg	cgc	ctg	atg	agg	gag	ctc	aac	cag	atg	cag	cgc	gag	6399
		Arg	Ala	Arg	Arg	Leu	Met	Arg	Glu	Leu	Asn	Gln	Met	Gln	Arg	Glu	
		2120						2125					2130				
70		tac	gtg	gag	ctc	agg	aaa	cag	atg	aca	aac	caa	aag	gat	ttg	gaa	6444
		Tyr	Val	Glu	Leu	Arg	Lys	Gln	Met	Thr	Asn	Gln	Lys	Asp	Leu	Glu	
		2135						2140					2145				
75		aga	aga	cag	atg	gaa	atc	agt	gat	gcg	atg	caa	gca	ctt	aaa	tgt	6489
		Arg	Arg	Gln	Met	Glu	Ile	Ser	Asp	Ala	Met	Gln	Ala	Leu	Lys	Cys	

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		2150				2155					2160						
5		gag Glu	gtg Val	aaa Lys	gat Asp	gaa Glu	atc Ile	cga Arg	acc Thr	agc Ser	ctg Leu	aag Lys	aat Asn	ctc Leu	aac Asn	cag Gln	6534
		2165						2170					2175				
		ttt Phe	ctt Leu	cca Pro	gag Glu	ctg Leu	cca Pro	gcg Ala	gac Asp	ctg Leu	gag Glu	gcc Ala	ctt Leu	ctg Leu	gaa Glu	agg Arg	6579
		2180						2185					2190				
10		aat Asn	gag Glu	aac Asn	ctt Leu	gga Gly	gga Gly	ggc Gly	ttg Leu	gag Glu	agc Ser	ttg Leu	aaa Lys	gag Glu	aat Asn	ttc Phe	6624
		2195						2200					2205				
15		ccg Pro	ttt Phe	acc Thr	gtg Val	agc Ser	gac Asp	aga Arg	cca Pro	tca Ser	tct Ser	tgc Cys	gaa Glu	gag Glu	aaa Lys	ctg Leu	6669
		2210						2215					2220				
		aat Asn	ttt Phe	ggc Gly	cag Gln	gct Ala	cac His	gtg Val	gcg Ala	gat Asp	gaa Glu	cag Gln	tgg Trp	cgg Arg	gga Gly	gag Glu	6714
		2225						2230					2235				
20		gca Ala	ctc Leu	cgg Arg	gag Glu	aag Lys	ctg Leu	cgc Arg	cac His	cgc Arg	gag Glu	gac Asp	cgg Arg	ctc Leu	aag Lys	gcc Ala	6759
		2240						2245					2250				
25		cag Gln	ctg Leu	cgc Arg	cgc Arg	tgc Cys	atg Met	tcc Ser	aag Lys	cag Gln	gcc Ala	gag Glu	gtg Val	ctg Leu	agc Ser	gag Glu	6804
		2255						2260					2265				
		ggc Gly	cgg Arg	cgg Arg	cgc Arg	acg Thr	gag Glu	ggg Gly	acc Thr	ctg Leu	cac His	agc Ser	ctg Leu	cgg Arg	cgg Arg	cag Gln	6849
		2270						2275					2280				
30		gtg Val	gac Asp	gcc Ala	ctg Leu	ggc Gly	gag Glu	ctg Leu	gtc Val	acc Thr	agc Ser	act Thr	tcc Ser	ggg Gly	gac Asp	tcc Ser	6894
		2285						2290					2295				
35		gcg Ala	tcc Ser	acc Thr	cgc Arg	agt Ser	ctg Leu	tcg Ser	cgc Arg	acc Thr	gag Glu	ggc Gly	tcg Ser	ctc Leu	gcc Ala	gag Glu	6939
		2300						2305					2310				
		gac Asp	gaa Glu	ccg Pro	ccg Pro	ggg Gly	ccc Pro	agc Ser	cag Gln	gag Glu	ctg Leu	cac His	gtg Val	ctg Leu	ggg Gly	tcg Ser	6984
		2315						2320					2325				
		ggc Gly	ggc Gly	agc Ser	gac Asp	cga Arg	ggt Gly	gga Gly	gga Gly	cgg Arg	ggc Gly	ggg Gly	ggc Gly	agg Arg	aag Lys	ggc Gly	7029
		2330						2335					2340				
45		ctt Leu	tcc Ser	cga Arg	cgc Arg	cgc Arg	cgc Arg	tgg Trp	aac Asn	cac His	gga Gly	gaa Glu	gcg Ala	cgc Arg	ctc Leu	ggc Gly	7074
		2345						2350					2355				
50		ccg Pro	cgg Arg	agg Arg	ccc Pro	cca Pro	cgg Arg	gag Glu	ggg Gly	gca Ala	ggg Gly	cgg Arg	ggc Gly	gcg Ala	gcc Ala	ttc Phe	7119
		2360						2365					2370				
		cga Arg	gcc Ala	ttg Leu	gtc Val	tcc Ser	tgc Cys	tcc Ser	cgc Arg	cct Pro	gca Ala	gag Glu	ctc Leu	ccg Pro	gcg Ala	gct Ala	7164
		2375						2380					2385				
55		ccc Gly	ccg Gly	agg Ser	ccc Ser	gtc Gly	gcc Gly	gcg Gly	gct Gly	gga Gly	cgc Gly	gca Gly	ccg Gly	acc Gly	ctg Gly	agg Gly	7209

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	Pro	Pro	Arg	Pro	Val	Ala	Ala	Ala	Gly	Arg	Ala	Pro	Thr	Leu	Arg	
	2390						2395					2400				
5	acc	cgg	agg	acc	cgg	agg	ccc	ggc	gtc	ccc	tcg	gaa	cgc	ttc	ctc	7254
	Thr	Arg	Arg	Thr	Arg	Arg	Pro	Gly	Val	Pro	Ser	Glu	Arg	Phe	Leu	
	2405						2410					2415				
10	cgc	gtc	cgc	gga	cac	cag	gct	cac	ggg	aag	gcg	cgt	cca	tgc	ggg	7299
	Arg	Val	Arg	Gly	His	Gln	Ala	His	Gly	Lys	Ala	Arg	Pro	Cys	Gly	
	2420						2425					2430				
	aag	agc	cgc	gag	cgg	aac	ccg	gat	gcc	cgg	gct	ggg	ctc	tgg	gcc	7344
	Lys	Ser	Arg	Glu	Arg	Asn	Pro	Asp	Ala	Arg	Ala	Gly	Leu	Trp	Ala	
	2435						2440					2445				
15	ttg	gaa	acg	tgt	tgc	cgt	aaa	agc	agc	gcc	cgc	ggc	tgc	gga	ctt	7389
	Leu	Glu	Thr	Cys	Cys	Arg	Lys	Ser	Ser	Ala	Arg	Gly	Cys	Gly	Leu	
	2450						2455					2460				
20	gaa	gcc	ccg	aac	tgc	cgc	cgt	gcc	cgg	tgc	gga	gcg	agc	gtg	cgg	7434
	Glu	Ala	Pro	Asn	Cys	Arg	Arg	Ala	Arg	Cys	Gly	Ala	Ser	Val	Arg	
	2465						2470					2475				
	tac	cct	ctc	gtg	cct	cgg	ggc	cgg	act	gga	cga	ggg	gcc	gtg	acc	7479
	Tyr	Pro	Leu	Val	Pro	Arg	Gly	Arg	Thr	Gly	Arg	Gly	Ala	Val	Thr	
	2480						2485					2490				
25	ccg	tgg	ggc	cgc	ctg	cag	tcc	cga	ggg	acg	cgg	acc	acc	ccc	cgg	7524
	Pro	Trp	Gly	Arg	Leu	Gln	Ser	Arg	Gly	Thr	Arg	Thr	Thr	Pro	Arg	
	2495						2500					2505				
30	ccg	gtg	cga	cgg	gag	cat	ccc	cag	cac	cag	gaa	agg	ccc	cca	ggg	7569
	Pro	Val	Arg	Arg	Glu	His	Pro	Gln	His	Gln	Glu	Arg	Pro	Pro	Gly	
	2510						2515					2520				
35	cgc	gtt	acc	gcg	gcc	cac	act	gag	acc	gcc	cct	ccc	cgc	cgg	gtg	7614
	Arg	Val	Thr	Ala	Ala	His	Thr	Glu	Thr	Ala	Pro	Pro	Arg	Arg	Val	
	2525						2530					2535				
40	ttc	cac	gcg	cga	gta	gca	gtc	ggg	gag	gtc	agc	ctc	ggg	ccc	ggc	7659
	Phe	His	Ala	Arg	Val	Ala	Val	Gly	Glu	Val	Ser	Leu	Gly	Pro	Gly	
	2540						2545					2550				
45	cgc	ggt	ctc	gag	cga	aca	cgg	ggc	ggg	ggc	ggg	ggg	gcg	ggg	gcg	7704
	Arg	Gly	Leu	Glu	Arg	Thr	Arg	Gly	Gly	Gly	Gly	Gly	Ala	Gly	Ala	
	2555						2560					2565				
50	gga	ctc	ctc	gca	gag	gcc	gcg	gcc	acg	gcc	cgg	tgc	gca	gac	ccc	7749
	Gly	Leu	Leu	Ala	Glu	Ala	Ala	Ala	Thr	Ala	Arg	Cys	Ala	Asp	Pro	
	2570						2575					2580				
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5	Ser	Ser	His	Ser	Pro	Ser	Pro	Pro	Ser	Leu	Thr	Ser	Asn	Met	Arg	Ser	
				20					25					30			
	Arg	Ser	Leu	Ser	Pro	Leu	Ser	Gly	Ser	Glu	Thr	Leu	Pro	Phe	His	Phe	
10			35					40					45				
	Gly	Gly	Pro	Trp	His	Glu	Gln	Val	Glu	Ile	Thr	Asp	Glu	Ser	Thr	Val	
		50					55					60					
15	Val	Leu	Asp	Tyr	Gln	Asp	His	Lys	Glu	Ala	Asp	Ser	His	Ala	Gly	Val	
	65					70					75					80	
	Arg	Tyr	Ile	Thr	Glu	Ala	Leu	Val	Arg	Lys	Leu	Thr	Lys	Gln	Asp	Asn	
20					85					90					95		
	Leu	Ala	Leu	Val	Lys	Ser	Leu	Asn	Leu	Ser	Leu	Ala	Lys	Gly	Gly	Gly	
25				100					105					110			
	Lys	Lys	Phe	Arg	Cys	Ile	Glu	Asn	Leu	Glu	Lys	Cys	Val	Lys	Leu	Glu	
			115					120					125				
30	Val	Leu	Asn	Leu	Ser	Tyr	Asn	Leu	Ile	Gly	Lys	Ile	Glu	Lys	Val	Asp	
		130					135						140				
	Lys	Leu	Leu	Lys	Leu	Arg	Glu	Leu	Asn	Leu	Ser	Tyr	Asn	Lys	Ile	Arg	
35		145				150					155					160	
	Lys	Ile	Glu	Gly	Ile	Glu	Asn	Leu	Tyr	Asn	Leu	Gln	Lys	Leu	Asn	Leu	
					165					170					175		
40	Ala	Gly	Asn	Glu	Ile	Glu	His	Ile	Pro	Val	Trp	Leu	Gly	Lys	Lys	Leu	
				180					185					190			
	Lys	Ser	Leu	Arg	Ile	Leu	Asn	Leu	Lys	Gly	Asn	Lys	Ile	Ser	Ser	Leu	
45			195					200					205				
	Gln	Asp	Val	Ser	Lys	Leu	Lys	Pro	Leu	Gln	Asp	Leu	Thr	Ser	Leu	Ile	
50		210					215					220					
	Leu	Leu	Glu	Asn	Pro	Val	Ala	Thr	Leu	Pro	His	Tyr	Ile	Gln	Phe	Thr	
	225					230					235					240	
55	Ile	Phe	His	Leu	Arg	Ser	Leu	Glu	Ser	Leu	Glu	Gly	Gln	Pro	Val	Thr	
					245					250					255		

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	Ser	Gln	Asp	Arg	Gln	Glu	Ala	Phe	Ala	Arg	Phe	Ser	Leu	Asp	Glu	Val	
					260				265					270			
5	Glu	Arg	Leu	Glu	Arg	Asp	Leu	Glu	Lys	Lys	Thr	Met	Glu	Thr	Glu	Glu	
			275					280					285				
10	Leu	Arg	Ser	Glu	Gln	Thr	Arg	Phe	Leu	Glu	Glu	Ile	Lys	Ser	Gln	Asp	
		290					295					300					
15	Lys	Leu	Asn	Lys	Ser	Leu	Lys	Glu	Glu	Ala	Arg	Leu	Gln	Lys	Gln	Ser	
	305					310					315					320	
20	Tyr	Glu	Glu	Leu	Glu	Ser	Asn	Leu	Asn	Thr	Lys	Asn	Glu	Leu	Leu	Lys	
					325					330					335		
25	Gln	Lys	Thr	Met	Glu	Leu	Met	Arg	Ala	Cys	Gln	Lys	Gln	Tyr	Glu	Met	
				340					345					350			
30	Glu	Gln	Glu	Leu	Ala	Phe	Tyr	Lys	Ile	Asp	Ala	Lys	Phe	Glu	Pro	Leu	
			355					360					365				
35	Asn	Tyr	Tyr	Pro	Ser	Glu	Tyr	Val	Glu	Ile	Asp	Lys	Thr	Pro	Asp	Glu	
	370						375					380					
40	Ser	Pro	Tyr	Ile	Gly	Lys	Ser	Arg	Tyr	Lys	Arg	Asn	Met	Phe	Thr	Thr	
	385					390					395					400	
45	Glu	Ser	Tyr	Ile	Ile	Ala	Asn	Ala	Gln	Thr	Val	Lys	Ile	Lys	Lys	Met	
					405					410					415		
50	Glu	Leu	Asp	Glu	Gly	Glu	Gln	Leu	Arg	Asn	Glu	His	Val	Asn	Leu	Gly	
				420					425					430			
55	Ala	Ser	Pro	Thr	Asp	Ile	Gln	Leu	Glu	Asp	Lys	Glu	Lys	Lys	Ile	Ser	
			435					440					445				
60	Ala	Ala	Gln	Thr	Arg	Leu	Ser	Glu	Leu	His	Asp	Glu	Ile	Glu	Lys	Ala	
		450					455					460					
65	Glu	Gln	Gln	Ile	Leu	Arg	Ala	Thr	Glu	Glu	Phe	Lys	Gln	Leu	Glu	Glu	
	465					470					475					480	
70	Ala	Ile	Gln	Leu	Lys	Lys	Ile	Ser	Glu	Ala	Glu	Lys	Asp	Leu	Leu	Phe	
					485					490					495		
75	Lys	Gln	Leu	Ser	Gly	Arg	Ile	Gln	Leu	Leu	Asn	Lys	Leu	Arg	Gln	Glu	
				500					505					510			

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	Ala	Val	Asp	Leu	Glu	Thr	Gln	Met	Glu	Lys	Gln	Arg	Gln	Glu	Ile	Gly
			515					520					525			
5	Glu	Lys	Gln	Asn	Glu	Ile	Lys	Asp	Leu	Glu	Ile	Val	Thr	Asp	Ser	Leu
			530				535					540				
10	Asp	Ser	Arg	Asp	Pro	Lys	His	Cys	His	Met	Lys	Ala	Gln	Lys	Arg	Gly
	545					550					555					560
15	Lys	Glu	Gln	Gln	Leu	Asp	Ile	Met	Asn	Lys	Gln	Tyr	Lys	Gln	Leu	Glu
					565					570					575	
20	Ser	Arg	Leu	Asp	Glu	Ile	Leu	Ser	Arg	Ile	Ala	Lys	Glu	Thr	Glu	Glu
			580						585					590		
25	Ile	Lys	Asp	Leu	Glu	Glu	Gln	Leu	Thr	Glu	Gly	Gln	Ile	Ala	Ala	Asn
			595					600					605			
30	Glu	Ala	Leu	Lys	Lys	Asp	Leu	Glu	Ser	Val	Ile	Ser	Gly	Leu	Gln	Glu
		610					615					620				
35	Tyr	Leu	Glu	Thr	Val	Lys	Gly	Gln	Ala	Arg	Gln	Ala	Gln	Asn	Glu	Cys
	625					630					635					640
40	Arg	Lys	Leu	Gln	Asp	Glu	Lys	Glu	Thr	Leu	Leu	Gln	Arg	Leu	Ser	Glu
				645						650					655	
45	Val	Glu	Gln	Glu	Arg	Asp	Gln	Leu	Glu	Ile	Val	Ala	Ile	Asp	Ala	Glu
				660					665					670		
50	Asn	Met	Arg	Lys	Glu	Leu	Ala	Glu	Leu	Glu	Asn	Ala	Leu	Gln	Glu	Gln
		675						680					685			
55	His	Glu	Val	Asn	Ile	Ser	Leu	Gln	Gln	Thr	Gln	Gly	Asp	Leu	Ser	Ala
		690					695					700				
60	Tyr	Glu	Ala	Glu	Leu	Glu	Ala	Gln	Leu	Lys	Ile	Arg	Asp	Ala	Glu	Ala
	705					710					715					720
65	Asn	Gln	Leu	Lys	Glu	Glu	Leu	Glu	Lys	Leu	Arg	Arg	Leu	Ser	Gln	Leu
				725						730					735	
70	Glu	Gln	Ser	Ala	Leu	Gln	Ala	Glu	Leu	Glu	Lys	Glu	Lys	Gln	Ala	Phe
			740						745					750		
75	Lys	Thr	Ala	Val	Lys	Lys	Ala	Gln	Leu	Ser	Glu	Gly	Lys	Asp	Gln	Glu

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	755					760					765					
5	Asn	Ser	Glu	Leu	Arg	Thr	Gln	Leu	Gln	Gln	Leu	Gln	Asp	Asp	Asn	Asp
	770						775					780				
10	Leu	Leu	Lys	Gln	Gln	Leu	Lys	Asp	Phe	Gln	Ser	His	Leu	Asn	His	Val
	785					790					795					800
15	Val	Asp	Gly	Leu	Ile	Arg	Pro	Glu	Glu	Val	Ala	Ala	Cys	Val	Asp	Glu
					805					810					815	
20	Leu	Arg	Lys	Lys	Leu	Lys	Ser	Gly	Ala	Gly	Glu	Met	Arg	Ile	His	Thr
				820					825					830		
25	Pro	Ser	Asp	Val	Leu	Gly	Lys	Ser	Leu	Ala	Asp	Leu	Gln	Lys	Gln	Phe
			835					840					845			
30	Ser	Glu	Ile	Leu	Ala	Arg	Ser	Gln	Trp	Glu	Arg	Gln	Glu	Ala	Gln	Val
	850						855					860				
35	Arg	Glu	Arg	Lys	Leu	Gln	Glu	Glu	Met	Ala	Leu	Gln	Gln	Glu	Lys	Leu
	865					870					875					880
40	Ala	Ser	Gly	Gln	Glu	Glu	Phe	Arg	His	Ala	Cys	Glu	Arg	Ala	Leu	Glu
					885					890					895	
45	Ala	Arg	Ile	Ser	Phe	Asp	Lys	Arg	Gln	His	Glu	Ala	Arg	Ile	Gln	Gln
				900					905					910		
50	Leu	Glu	Asn	Glu	Ile	His	Tyr	Leu	Gln	Glu	Asn	Leu	Lys	Ser	Met	Glu
			915					920					925			
55	Glu	Ile	Gln	Gly	Leu	Thr	Asp	Leu	Gln	Leu	Gln	Glu	Ala	Asp	Glu	Glu
		930					935					940				
60	Lys	Glu	Arg	Ile	Leu	Ala	Gln	Leu	Arg	Glu	Leu	Glu	Lys	Lys	Lys	Lys
	945					950					955					960
65	Leu	Glu	Asp	Ala	Lys	Ser	Gln	Glu	Gln	Phe	Leu	Gly	Leu	Asp	Arg	Glu
					965					970					975	
70	Leu	Lys	Lys	Leu	Lys	Lys	Ala	Val	Ala	Ala	Ser	Asp	Lys	Leu	Ala	Thr
				980					985					990		
75	Ala	Glu	Leu	Thr	Ile	Ala	Lys	Asp	Gln	Leu	Lys	Ser	Leu	His	Gly	Thr
			995					1000						1005		

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	Val	Met	Lys	Ile	Asn	Gln	Glu	Arg	Ala	Glu	Glu	Leu	Gln	Glu	Thr
	1010						1015					1020			
5	Glu	Arg	Phe	Ser	Arg	Lys	Ala	Ala	Gln	Ala	Ala	Arg	Asp	Leu	Ile
	1025						1030					1035			
10	Arg	Ala	Glu	Ala	Glu	Ile	Glu	Leu	Leu	Gln	Lys	Leu	Leu	Arg	Asp
	1040						1045					1050			
15	Lys	Glu	Glu	Gln	Phe	Arg	Asn	Glu	Ile	Glu	Lys	Val	Asp	Val	Gly
	1055						1060					1065			
20	Ser	Gly	Gly	Ala	Lys	Ser	Gln	Met	Leu	Glu	Met	Glu	Lys	Leu	Asn
	1070						1075					1080			
25	Glu	Thr	Met	Glu	Arg	Gln	Arg	Thr	Glu	Ile	Ala	Arg	Leu	Arg	Asn
	1085						1090					1095			
30	Leu	Leu	Asp	Leu	Thr	Gly	Ala	Asp	Asn	Lys	Gly	Asn	Phe	Glu	Asn
	1100						1105					1110			
35	Val	Leu	Glu	Glu	Ile	Ala	Glu	Leu	Arg	Arg	Glu	Val	Ser	His	Gln
	1115						1120					1125			
40	Asn	Asp	Tyr	Ile	Ser	Ser	Met	Thr	Asp	Pro	Phe	Lys	Arg	Arg	Gly
	1130						1135					1140			
45	Tyr	Trp	Tyr	Phe	Met	Pro	Pro	Pro	Ser	Ser	Ser	Lys	Val	Ser	Ser
	1145						1150					1155			
50	His	Ser	Ser	Gln	Ala	Thr	Lys	Asp	Ser	Gly	Val	Gly	Leu	Lys	Tyr
	1160						1165					1170			
55	Thr	Ala	Ser	Thr	Pro	Val	Arg	Lys	Pro	His	Arg	Gly	Arg	Gln	Asp
	1175						1180					1185			
60	Gly	Lys	Glu	Asn	Ser	Gly	Pro	Pro	Pro	Ala	Ser	Gly	Tyr	Trp	Val
	1190						1195					1200			
65	Tyr	Ser	Pro	Ile	Arg	Ser	Gly	Leu	His	Lys	Ser	Phe	Ser	Asn	Arg
	1205						1210					1215			
70	Asp	Ala	Asp	Ser	Gly	Gly	Asp	Ser	Gln	Glu	Glu	Ser	Glu	Leu	Asp
	1220						1225					1230			
75	Asp	Gln	Glu	Asp	His	Pro	Phe	Val	Pro	Pro	Pro	Gly	Tyr	Met	Met
	1235						1240					1245			

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	Tyr	Thr	Val	Phe	Pro	Asp	Gly	Ser	Pro	Val	Pro	Gln	Gly	Met	Ala
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5	Leu	Tyr	Ala	Pro	Pro	Pro	Pro	Leu	Pro	Asn	Asn	Ser	Gln	Pro	Leu
	1265						1270					1275			
10	Asp	Leu	Gly	Thr	Val	Val	Tyr	Gly	Pro	Pro	Pro	Val	Gly	Ala	Pro
	1280						1285					1290			
15	Ile	Val	Tyr	Gly	Pro	Pro	Pro	Pro	Asn	Phe	Ser	Val	Pro	Leu	Ile
	1295						1300					1305			
20	Pro	Val	Gly	Val	Leu	His	Cys	Asn	Val	Pro	Glu	His	His	Asn	Leu
	1310						1315					1320			
25	Glu	Asn	Glu	Val	Ser	Arg	Leu	Glu	Asp	Ile	Met	Gln	His	Leu	Lys
	1325						1330					1335			
30	Ser	Gly	Lys	Arg	Glu	Gln	Cys	Met	Lys	Thr	Pro	Lys	Leu	Gln	Ser
	1340						1345					1350			
35	Glu	Lys	Glu	Leu	Ala	Glu	Leu	Gln	His	Asn	Ile	Asp	Gly	Leu	Leu
	1355						1360					1365			
40	Gln	Glu	Lys	Lys	Asp	Leu	Glu	His	Glu	Val	Glu	Glu	Leu	His	Arg
	1370						1375					1380			
45	Thr	Ile	Gln	Lys	His	Gln	Gln	Arg	Lys	Asp	Phe	Ile	Asp	Gly	Asn
	1385						1390					1395			
50	Val	Glu	Ser	Leu	Val	Asn	Asp	Leu	Glu	Ile	Glu	Lys	Ser	Leu	Lys
	1400						1405					1410			
55	His	His	Glu	Asp	Ile	Val	Asp	Glu	Ile	Glu	Cys	Ile	Glu	Arg	Thr
	1415						1420					1425			
60	Leu	Leu	Lys	Arg	Arg	Ala	Glu	Leu	Arg	Glu	Ala	Asp	Arg	Leu	Leu
	1430						1435					1440			
65	Thr	Glu	Ala	Glu	Ser	Glu	Leu	Ser	Cys	Thr	Lys	Glu	Lys	Thr	Lys
	1445						1450					1455			
70	His	Ala	Val	Glu	Lys	Phe	Thr	Asp	Ala	Lys	Arg	Asn	Leu	Leu	Gln
	1460						1465					1470			
75	Thr	Glu	Lys	Asp	Ala	Glu	Glu	Leu	Glu	Arg	Arg	Ala	Gln	Glu	Thr
	1475						1480					1485			

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	Ala	Ile	Asn	Leu	Val	Lys	Ala	Asp	Gln	Gln	Leu	Arg	Leu	Leu	Gln
	1490						1495					1500			
5	Ala	Asp	Thr	Lys	Asp	Leu	Glu	Gln	His	Lys	Met	Glu	Gln	Glu	Glu
	1505						1510					1515			
10	Ile	Leu	Lys	Glu	Ile	Asn	Lys	Val	Val	Ala	Ala	Lys	Asp	Ser	Asp
	1520						1525					1530			
15	Phe	Gln	Ser	Leu	Asn	Lys	Lys	Lys	Glu	Val	Leu	Thr	Gly	Glu	Leu
	1535						1540					1545			
20	Gln	Lys	Leu	Gln	Lys	Asp	Ile	Glu	Thr	Ala	Arg	His	Asn	Glu	Asp
	1550						1555					1560			
25	Gln	His	Leu	Gln	Val	Leu	Lys	Glu	Ser	Glu	Thr	Leu	Leu	Gln	Ala
	1565						1570					1575			
30	Lys	Lys	Ala	Glu	Leu	Glu	Asn	Leu	Lys	Ser	Gln	Val	Ser	Gly	Gln
	1580						1585					1590			
35	Gln	Gln	Glu	Met	Ala	Val	Leu	Asp	Arg	Glu	Leu	Gly	His	Lys	Lys
	1595						1600					1605			
40	Glu	Glu	Leu	His	Leu	Leu	Gln	Glu	Ser	Met	Val	Gln	Ala	Lys	Ala
	1610						1615					1620			
45	Asp	Leu	Gln	Glu	Ala	Leu	Arg	Leu	Gly	Glu	Ser	Glu	Val	Thr	Glu
	1625						1630					1635			
50	Lys	Cys	Asn	His	Ile	Arg	Glu	Val	Lys	Ser	Leu	Leu	Glu	Glu	Leu
	1640						1645					1650			
55	Ser	Phe	Gln	Lys	Gly	Glu	Leu	Asn	Val	Gln	Ile	Ser	Glu	Lys	Lys
	1655						1660					1665			
60	Thr	Gln	Leu	Ala	Leu	Ile	Lys	Gln	Glu	Ile	Glu	Lys	Glu	Glu	Asp
	1670						1675					1680			
65	Asn	Leu	Gln	Val	Val	Leu	Gly	Gln	Met	Ser	Lys	His	Lys	Thr	Glu
	1685						1690					1695			
70	Leu	Lys	Asn	Ile	Leu	Asp	Met	Leu	Gln	Leu	Glu	Asn	Asn	Glu	Leu
	1700						1705					1710			
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	1715					1720						1725			
5	Lys Thr	Arg Val	Glu Val	Leu	Glu Glu	Lys Leu	Glu	Leu Glu	Ser						
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	Leu Gln	Gln Ala	Ala Leu	Arg	Gln Arg	Gly Glu	Ile	Glu Trp	Gln						
10	1745				1750			1755							
	Lys Gln	Leu Leu	Gln Arg	Asn	Thr Gln	Glu Val	Glu	Arg Met	Thr						
	1760				1765			1770							
15	Ala Glu	Thr Arg	Ala Leu	Gln	Ser Cys	Val Glu	Ser	Leu Cys	Lys						
	1775				1780			1785							
	Glu Lys	Gln Asp	Leu Glu	Glu	Lys Gln	Asp Ser	Trp	Glu Lys	Lys						
20	1790				1795			1800							
	Leu Ala	Gln Thr	Lys Arg	Val	Leu Ala	Ala Ala	Glu	Glu Asp	Ser						
	1805				1810			1815							
25	Glu Met	Glu Arg	Ala Arg	Leu	Glu Lys	Leu Glu	Leu	Asp Ala	Arg						
	1820				1825			1830							
30	Lys Leu	Gln Gln	Glu Leu	Asp	Gln Arg	Asn Arg	Glu	Lys Leu	Ser						
	1835				1840			1845							
	Leu His	Gln Asp	Leu Ala	Val	Val Gln	Gln Gln	Leu	Gln Glu	Lys						
35	1850				1855			1860							
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	1865				1870			1875							
40	Glu His	Leu Asp	Leu Ala	Glu	Gln Glu	Val Leu	Cys	Thr Thr	Lys						
	1880				1885			1890							
45	Arg Lys	Asp Ala	Leu Leu	Ser	Glu Gln	Thr Arg	Leu	Glu Lys	Asp						
	1895				1900			1905							
	Val Gly	Glu Trp	Thr Lys	Lys	Phe Glu	Asp Cys	Gln	Lys Glu	Gly						
50	1910				1915			1920							
	Glu Thr	Lys Gln	Gln Gln	Leu	Gln Gly	Leu Gln	Lys	Glu Ile	Glu						
	1925				1930			1935							
55	Gly Asn	Glu Ala	Lys Leu	Ala	Gln Gln	Glu Met	Met	Phe Gln	Arg						
	1940				1945			1950							

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	Leu 1955	Gln	Lys	Glu	Arg	Glu	Cys 1960	Glu	Glu	Lys	Lys	Leu 1965	Glu	Ala	Ser
5	Lys 1970	Val	Thr	Leu	Lys	Glu	Gln 1975	Gln	Gln	Gln	Leu	Glu 1980	Lys	Glu	Leu
10	Met 1985	Glu	Gln	Lys	Gly	Lys	Leu 1990	Asp	Gln	Val	Leu	Ala 1995	Lys	Leu	Leu
	Val 2000	Ala	Glu	Glu	Arg	Val	Arg 2005	Thr	Leu	Gln	Glu	Glu 2010	Gly	Arg	Trp
15	Ser 2015	Glu	Thr	Leu	Glu	Lys	Thr 2020	Leu	Ser	Gln	Thr	Lys 2025	Arg	Gln	Leu
20	Ser 2030	Glu	Arg	Glu	Gln	Gln	Leu 2035	Leu	Ala	Lys	Ser	Asp 2040	Glu	Leu	Leu
25	Ala 2045	Leu	Gln	Lys	Glu	Thr	Asp 2050	Ser	Met	Arg	Ala	Asp 2055	Phe	Ser	Leu
	Leu 2060	Arg	Asn	Gln	Phe	Leu	Thr 2065	Glu	Arg	Lys	Lys	Ala 2070	Glu	Lys	Gln
30	Val 2075	Ala	Ser	Leu	Lys	Glu	Ala 2080	Leu	Lys	Ile	Gln	Arg 2085	Ser	Gln	Leu
35	Glu 2090	Lys	Asn	Leu	Leu	Glu	Gln 2095	Lys	Gln	Glu	Asn	Ser 2100	Cys	Met	Gln
40	Arg 2105	Glu	Met	Ala	Thr	Ile	Glu 2110	Gln	Val	Ala	Gln	Asp 2115	Asn	His	Glu
	Arg 2120	Ala	Arg	Arg	Leu	Met	Arg 2125	Glu	Leu	Asn	Gln	Met 2130	Gln	Arg	Glu
45	Tyr 2135	Val	Glu	Leu	Arg	Lys	Gln 2140	Met	Thr	Asn	Gln	Lys 2145	Asp	Leu	Glu
50	Arg 2150	Arg	Gln	Met	Glu	Ile	Ser 2155	Asp	Ala	Met	Gln	Ala 2160	Leu	Lys	Cys
	Glu 2165	Val	Lys	Asp	Glu	Ile	Arg 2170	Thr	Ser	Leu	Lys	Asn 2175	Leu	Asn	Gln
55	Phe 2180	Leu	Pro	Glu	Leu	Pro	Ala 2185	Asp	Leu	Glu	Ala	Leu 2190	Leu	Glu	Arg

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	Asn	Glu	Asn	Leu	Gly	Gly	Gly	Leu	Glu	Ser	Leu	Lys	Glu	Asn	Phe
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	2225						2230					2235			
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	2240						2245					2250			
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25	Gly	Arg	Arg	Arg	Thr	Glu	Gly	Thr	Leu	His	Ser	Leu	Arg	Arg	Gln
	2270						2275					2280			
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35	Ala	Ser	Thr	Arg	Ser	Leu	Ser	Arg	Thr	Glu	Gly	Ser	Leu	Ala	Glu
	2300						2305					2310			
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	2315						2320					2325			
45	Gly	Gly	Ser	Asp	Arg	Gly	Gly	Gly	Arg	Gly	Gly	Gly	Arg	Lys	Gly
	2330						2335					2340			
50	Leu	Ser	Arg	Arg	Arg	Arg	Trp	Asn	His	Gly	Glu	Ala	Arg	Leu	Gly
	2345						2350					2355			
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	2375						2380					2385			
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	2405						2410					2415			
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5	Leu Glu Thr Cys Cys Arg Lys Ser Ser Ala Arg Gly Cys Gly Leu	
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	2465 2470 2475	
15	Tyr Pro Leu Val Pro Arg Gly Arg Thr Gly Arg Gly Ala Val Thr	
	2480 2485 2490	
20	Pro Trp Gly Arg Leu Gln Ser Arg Gly Thr Arg Thr Thr Pro Arg	
	2495 2500 2505	
25	Pro Val Arg Arg Glu His Pro Gln His Gln Glu Arg Pro Pro Gly	
	2510 2515 2520	
30	Arg Val Thr Ala Ala His Thr Glu Thr Ala Pro Pro Arg Arg Val	
	2525 2530 2535	
35	Phe His Ala Arg Val Ala Val Gly Glu Val Ser Leu Gly Pro Gly	
	2540 2545 2550	
40	Arg Gly Leu Glu Arg Thr Arg Gly Gly Gly Gly Gly Ala Gly Ala	
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	Lys Ile Phe Ser Lys Ala Lys Ile Pro Ser Ser Ser His Ser Pro Ile	

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15	gtt gag att gca gat gaa aac aat atg ctt ttg gac tat caa gac cat Val Glu Ile Ala Asp Glu Asn Asn Met Leu Leu Asp Tyr Gln Asp His 60 65 70	244		
20	aaa gga gct gat tca cat gca gga gtt aga tat att aca gag gcc ctc Lys Gly Ala Asp Ser His Ala Gly Val Arg Tyr Ile Thr Glu Ala Leu 75 80 85	292		
25	att aaa aaa ctt act aaa cag gat aat ttg gct ttg ata aaa tct ctg Ile Lys Lys Leu Thr Lys Gln Asp Asn Leu Ala Leu Ile Lys Ser Leu 90 95 100	340		
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35	aat ttg gaa aaa tgt gtt aaa ctt gaa gta ctg aat ctc agc tat aat Asn Leu Glu Lys Cys Val Lys Leu Glu Val Leu Asn Leu Ser Tyr Asn 120 125 130 135	436		
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45	ctc aac tta tca tat aac aaa atc agc aaa att gaa ggc ata gaa aat Leu Asn Leu Ser Tyr Asn Lys Ile Ser Lys Ile Glu Gly Ile Glu Asn 155 160 165	532		
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65	ccg ctt caa gat ttg att tct ctg atc cta gtt gaa aat cca gtt gtg Pro Leu Gln Asp Leu Ile Ser Leu Ile Leu Val Glu Asn Pro Val Val 220 225 230	724		
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	Glu	Glu	Ala	Met	Leu	Gln	Lys	Gln	Ser	Cys	Glu	Glu	Leu	Lys	Ser	Asp	
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	Leu	Asn	Thr	Lys	Asn	Glu	Leu	Leu	Lys	Gln	Lys	Thr	Ile	Glu	Leu	Thr	
			330					335					340				
25	cga	gca	tgt	cag	aag	caa	tat	gag	ctg	gaa	cag	gaa	ttg	gcc	ttt	tat	1108
	Arg	Ala	Cys	Gln	Lys	Gln	Tyr	Glu	Leu	Glu	Gln	Glu	Leu	Ala	Phe	Tyr	
		345					350					355					
30	aaa	att	gat	gct	aaa	ttt	gag	cca	cta	aat	tat	tat	cca	tca	gag	tat	1156
	Lys	Ile	Asp	Ala	Lys	Phe	Glu	Pro	Leu	Asn	Tyr	Tyr	Pro	Ser	Glu	Tyr	
	360					365					370					375	
35	gct	gaa	att	gat	aaa	gcc	cca	gat	gaa	agc	cct	tac	att	ggc	aaa	tcc	1204
	Ala	Glu	Ile	Asp	Lys	Ala	Pro	Asp	Glu	Ser	Pro	Tyr	Ile	Gly	Lys	Ser	
					380					385				390			
40	aga	tac	aag	aga	aat	atg	ttt	gcc	aca	gag	agt	tat	att	att	gac	agt	1252
	Arg	Tyr	Lys	Arg	Asn	Met	Phe	Ala	Thr	Glu	Ser	Tyr	Ile	Ile	Asp	Ser	
				395					400					405			
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	Ala	Gln	Ala	Val	Gln	Ile	Lys	Lys	Met	Glu	Pro	Asp	Glu	Gln	Leu	Arg	
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	Asn	Asp	His	Met	Asn	Leu	Arg	Gly	His	Thr	Pro	Leu	Asp	Thr	Gln	Leu	
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	Glu	Asp	Lys	Glu	Lys	Lys	Ile	Ser	Ala	Ala	Gln	Thr	Arg	Leu	Ser	Glu	
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60	ctg	cat	gat	gaa	ata	gaa	aag	gca	gaa	caa	caa	att	ttg	aga	gct	act	1444
	Leu	His	Asp	Glu	Ile	Glu	Lys	Ala	Glu	Gln	Gln	Ile	Leu	Arg	Ala	Thr	
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	Glu	Glu	Phe	Lys	Gln	Leu	Glu	Glu	Ala	Ile	Gln	Leu	Lys	Lys	Ile	Ser	
				475					480					485			
70	gaa	gca	ggg	aaa	gac	ctt	ctt	tac	aag	cag	ttg	agt	ggt	aga	cta	caa	1540
	Glu	Ala	Gly	Lys	Asp	Leu	Leu	Tyr	Lys	Gln	Leu	Ser	Gly	Arg	Leu	Gln	
			490					495					500				
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	Leu	Val	Asn	Lys	Leu	Arg	Gln	Glu	Ala	Leu	Asp	Leu	Glu	Leu	Gln	Met	
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		520					525					530					535	
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		Asn	Lys	Gln	Tyr	Gln	Gln	Leu	Glu	Ser	Arg	Leu	Asp	Glu	Ile	Leu	Ser	
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		Arg	Ile	Ala	Lys	Glu	Thr	Glu	Glu	Ile	Lys	Asp	Leu	Glu	Glu	Gln	Leu	
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25		act	gaa	ggc	cag	ata	gca	gca	aat	gaa	gcc	ctg	aag	aag	gat	tta	gaa	1876
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		600					605					610				615		
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		Gly	Val	Ile	Ser	Gly	Leu	Gln	Glu	Tyr	Leu	Gly	Thr	Ile	Lys	Gly	Gln	
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		Ala	Thr	Gln	Ala	Gln	Asn	Glu	Cys	Arg	Lys	Leu	Arg	Asp	Glu	Lys	Glu	
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		Thr	Leu	Leu	Gln	Arg	Leu	Thr	Glu	Val	Glu	Gln	Glu	Arg	Asp	Gln	Leu	
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55		cag	acc	cag	gga	gat	ctc	agt	gcc	tat	gaa	gct	gag	cta	gag	gct	cgg	2164
		Gln	Thr	Gln	Gly	Asp	Leu	Ser	Ala	Tyr	Glu	Ala	Glu	Leu	Glu	Ala	Arg	
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65		aaa	gta	aca	aga	ctt	acc	cag	tta	gaa	caa	tca	gcc	ctt	caa	gca	gaa	2260
		Lys	Val	Thr	Arg	Leu	Thr	Gln	Leu	Glu	Gln	Ser	Ala	Leu	Gln	Ala	Glu	
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		Leu	Glu	Lys	Glu	Arg	Gln	Ala	Leu	Lys	Asn	Ala	Leu	Gly	Lys	Ala	Gln	
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	825 830 835	
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	860 865 870	
30	atg gct ctg cag caa gag aaa ctg gca act gga caa gaa gag ttc agg	2692
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	875 880 885	
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	890 895 900	
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	Gln His Glu Ala Arg Ile Gln Gln Met Glu Asn Glu Ile His Tyr Leu	
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45	caa gaa aat cta aaa agt atg gag gaa atc caa ggc ctt aca gat ctc	2836
	Gln Glu Asn Leu Lys Ser Met Glu Glu Ile Gln Gly Leu Thr Asp Leu	
	920 925 930 935	
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	955 960 965	
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	985 990 995	
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20	gag att gca agg ctg cag aat gta cta gac ctc act gga agt gac Glu Ile Ala Arg Leu Gln Asn Val Leu Asp Leu Thr Gly Ser Asp 1090 1095 1100			3343
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10	cca Pro 1285	cct Pro	cct Pro	gct Ala	ggg Gly	gcc Ala 1290	ccc Pro	atg Met	gtg Val	tat Tyr	ggg Gly 1295	cct Pro	cca Pro	ccc Pro	ccc Pro	3928
	aac Asn 1300	ttc Phe	tcc Ser	atc Ile	ccc Pro	ttc Phe 1305	atc Ile	cct Pro	atg Met	ggg Gly	gtg Val 1310	ctg Leu	cat His	tgc Cys	aac Asn	3973
15	gtc Val 1315	cct Pro	gaa Glu	cac His	cat His	aac Asn 1320	tta Leu	gag Glu	aat Asn	gaa Glu	gtt Val 1325	tct Ser	aga Arg	tta Leu	gaa Glu	4018
20	gac Asp 1330	ata Ile	atg Met	cag Gln	cat His	tta Leu 1335	aaa Lys	tca Ser	aag Lys	aag Lys	cgg Arg 1340	gaa Glu	gaa Glu	agg Arg	tgg Trp	4063
25	atg Met 1345	aga Arg	gca Ala	tcc Ser	aag Lys	cgg Arg 1350	cag Gln	tcg Ser	gag Glu	aaa Lys	gaa Glu 1355	atg Met	gaa Glu	gaa Glu	ctg Leu	4108
	cat His 1360	cat His	aat Asn	att Ile	gat Asp	gat Asp 1365	ctt Leu	ttg Leu	caa Gln	gag Glu	aag Lys 1370	aaa Lys	agc Ser	tta Leu	gag Glu	4153
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	Arg	Ser	Leu	Ser	Pro	Leu	Ile	Gly	Ser	Glu	Thr	Leu	Pro	Phe	His	Ser
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5	Gly	Gly	Gln	Trp	Cys	Glu	Gln	Val	Glu	Ile	Ala	Asp	Glu	Asn	Asn	Met
		50					55					60				
10	Leu	Leu	Asp	Tyr	Gln	Asp	His	Lys	Gly	Ala	Asp	Ser	His	Ala	Gly	Val
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15	Arg	Tyr	Ile	Thr	Glu	Ala	Leu	Ile	Lys	Lys	Leu	Thr	Lys	Gln	Asp	Asn
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45	Ala	Gly	Asn	Glu	Ile	Glu	His	Ile	Pro	Val	Trp	Leu	Gly	Lys	Lys	Leu
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	Gln Gln Ile Leu Arg Ala Thr Glu Glu Phe Lys Gln Leu Glu Glu Ala 465 470 475 480			
	Ile Gln Leu Lys Lys Ile Ser Glu Ala Gly Lys Asp Leu Leu Tyr Lys 485 490 495			
	Gln Leu Ser Gly Arg Leu Gln Leu Val Asn Lys Leu Arg Gln Glu Ala 500 505 510			
	Leu Asp Leu Glu Leu Gln Met Glu Lys Gln Lys Gln Glu Ile Ala Gly 515 520 525			

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	Lys	Gln	Lys	Glu	Ile	Lys	Asp	Leu	Gln	Ile	Ala	Ile	Asp	Ser	Leu	Asp	
	530						535					540					
5	Ser	Lys	Asp	Pro	Lys	His	Ser	His	Met	Lys	Ala	Gln	Lys	Ser	Gly	Lys	
	545					550					555					560	
	Glu	Gln	Gln	Leu	Asp	Ile	Met	Asn	Lys	Gln	Tyr	Gln	Gln	Leu	Glu	Ser	
10					565					570					575		
	Arg	Leu	Asp	Glu	Ile	Leu	Ser	Arg	Ile	Ala	Lys	Glu	Thr	Glu	Glu	Ile	
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15	Lys	Asp	Leu	Glu	Glu	Gln	Leu	Thr	Glu	Gly	Gln	Ile	Ala	Ala	Asn	Glu	
			595					600					605				
	Ala	Leu	Lys	Lys	Asp	Leu	Glu	Gly	Val	Ile	Ser	Gly	Leu	Gln	Glu	Tyr	
20		610					615					620					
	Leu	Gly	Thr	Ile	Lys	Gly	Gln	Ala	Thr	Gln	Ala	Gln	Asn	Glu	Cys	Arg	
25	625					630					635					640	
	Lys	Leu	Arg	Asp	Glu	Lys	Glu	Thr	Leu	Leu	Gln	Arg	Leu	Thr	Glu	Val	
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30	Glu	Gln	Glu	Arg	Asp	Gln	Leu	Glu	Ile	Val	Ala	Met	Asp	Ala	Glu	Asn	
				660					665					670			
	Met	Arg	Lys	Glu	Leu	Ala	Glu	Leu	Glu	Ser	Ala	Leu	Gln	Glu	Gln	His	
35			675					680					685				
	Glu	Val	Asn	Ala	Ser	Leu	Gln	Gln	Thr	Gln	Gly	Asp	Leu	Ser	Ala	Tyr	
		690					695					700					
40	Glu	Ala	Glu	Leu	Glu	Ala	Arg	Leu	Asn	Leu	Arg	Asp	Ala	Glu	Ala	Asn	
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	Gln	Leu	Lys	Glu	Glu	Leu	Glu	Lys	Val	Thr	Arg	Leu	Thr	Gln	Leu	Glu	
45					725					730					735		
	Gln	Ser	Ala	Leu	Gln	Ala	Glu	Leu	Glu	Lys	Glu	Arg	Gln	Ala	Leu	Lys	
50				740					745					750			
	Asn	Ala	Leu	Gly	Lys	Ala	Gln	Phe	Ser	Glu	Glu	Lys	Glu	Gln	Glu	Asn	
		755						760					765				
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	770						775					780					

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	Leu	Lys	Gln	Gln	Leu	Lys	Asp	Phe	Gln	Asn	His	Leu	Asn	His	Val	Val	785	790	795	800
5	Asp	Gly	Leu	Val	Arg	Pro	Glu	Glu	Val	Ala	Ala	Arg	Val	Asp	Glu	Leu	805	810	815	
10	Arg	Arg	Lys	Leu	Lys	Leu	Gly	Thr	Gly	Glu	Met	Asn	Ile	His	Ser	Pro	820	825	830	
15	Ser	Asp	Val	Leu	Gly	Lys	Ser	Leu	Ala	Asp	Leu	Gln	Lys	Gln	Phe	Ser	835	840	845	
20	Glu	Ile	Leu	Ala	Arg	Ser	Lys	Trp	Glu	Arg	Asp	Glu	Ala	Gln	Val	Arg	850	855	860	
25	Glu	Arg	Lys	Leu	Gln	Glu	Glu	Met	Ala	Leu	Gln	Gln	Glu	Lys	Leu	Ala	865	870	875	880
30	Thr	Gly	Gln	Glu	Glu	Phe	Arg	Gln	Ala	Cys	Glu	Arg	Ala	Leu	Glu	Ala	885	890	895	
35	Arg	Met	Asn	Phe	Asp	Lys	Arg	Gln	His	Glu	Ala	Arg	Ile	Gln	Gln	Met	900	905	910	
40	Glu	Asn	Glu	Ile	His	Tyr	Leu	Gln	Glu	Asn	Leu	Lys	Ser	Met	Glu	Glu	915	920	925	
45	Ile	Gln	Gly	Leu	Thr	Asp	Leu	Gln	Leu	Gln	Glu	Ala	Asp	Glu	Glu	Lys	930	935	940	
50	Glu	Arg	Ile	Leu	Ala	Gln	Leu	Arg	Glu	Leu	Glu	Lys	Lys	Lys	Lys	Leu	945	950	955	960
55	Glu	Asp	Ala	Lys	Ser	Gln	Glu	Gln	Val	Phe	Gly	Leu	Asp	Lys	Glu	Leu	965	970	975	
60	Lys	Lys	Leu	Lys	Lys	Ala	Val	Ala	Thr	Ser	Asp	Lys	Leu	Ala	Thr	Ala	980	985	990	
65	Glu	Leu	Thr	Ile	Ala	Lys	Asp	Gln	Leu	Lys	Ser	Leu	His	Gly	Thr	Val	995	1000	1005	
70	Met	Lys	Ile	Asn	Gln	Glu	Arg	Ala	Glu	Glu	Leu	Gln	Glu	Ala	Glu		1010	1015	1020	
75	Arg	Phe	Ser	Arg	Lys	Ala	Ala	Gln	Ala	Ala	Arg	Asp	Leu	Thr	Arg		1025	1030	1035	

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	Ala	Glu	Ala	Glu	Ile	Glu	Leu	Leu	Gln	Asn	Leu	Leu	Arg	Gln	Lys
	1040						1045					1050			
5	Gly	Glu	Gln	Phe	Arg	Leu	Glu	Met	Glu	Lys	Thr	Gly	Val	Gly	Thr
	1055						1060					1065			
10	Gly	Ala	Asn	Ser	Gln	Val	Leu	Glu	Ile	Glu	Lys	Leu	Asn	Glu	Thr
	1070						1075					1080			
15	Met	Glu	Arg	Gln	Arg	Thr	Glu	Ile	Ala	Arg	Leu	Gln	Asn	Val	Leu
	1085						1090					1095			
20	Asp	Leu	Thr	Gly	Ser	Asp	Asn	Lys	Gly	Gly	Phe	Glu	Asn	Val	Leu
	1100						1105					1110			
25	Glu	Glu	Ile	Ala	Glu	Leu	Arg	Arg	Glu	Val	Ser	Tyr	Gln	Asn	Asp
	1115						1120					1125			
30	Tyr	Ile	Ser	Ser	Met	Ala	Asp	Pro	Phe	Lys	Arg	Arg	Gly	Tyr	Trp
	1130						1135					1140			
35	Tyr	Phe	Met	Pro	Pro	Pro	Pro	Ser	Ser	Lys	Val	Ser	Ser	His	Ser
	1145						1150					1155			
40	Ser	Gln	Ala	Thr	Lys	Asp	Ser	Gly	Val	Gly	Leu	Lys	Tyr	Ser	Ala
	1160						1165					1170			
45	Ser	Thr	Pro	Val	Arg	Lys	Pro	Arg	Pro	Gly	Gln	Gln	Asp	Gly	Lys
	1175						1180					1185			
50	Glu	Gly	Ser	Gln	Pro	Pro	Pro	Ala	Ser	Gly	Tyr	Trp	Val	Tyr	Ser
	1190						1195					1200			
55	Pro	Ile	Arg	Ser	Gly	Leu	His	Lys	Leu	Phe	Pro	Ser	Arg	Asp	Ala
	1205						1210					1215			
	Asp	Ser	Gly	Gly	Asp	Ser	Gln	Glu	Glu	Ser	Glu	Leu	Asp	Asp	Gln
	1220						1225					1230			
	Glu	Glu	Pro	Pro	Phe	Val	Pro	Pro	Pro	Gly	Tyr	Met	Met	Tyr	Thr
	1235						1240					1245			
	Val	Leu	Pro	Asp	Gly	Ser	Pro	Val	Pro	Gln	Gly	Met	Ala	Leu	Tyr
	1250						1255					1260			
	Ala	Pro	Pro	Pro	Pro	Leu	Pro	Asn	Asn	Ser	Arg	Pro	Leu	Thr	Pro

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	1265		1270		1275										
5	Gly Thr 1280	Val Val Tyr	Gly Pro 1285	Pro Pro Ala	Gly Ala 1290	Pro Met Val									
10	Tyr Gly 1295	Pro Pro Pro	Pro Asn 1300	Phe Ser Ile	Pro Phe 1305	Ile Pro Met									
15	Gly Val 1310	Leu His Cys	Asn Val 1315	Pro Glu His	His Asn 1320	Leu Glu Asn									
20	Glu Val 1325	Ser Arg Leu	Glu Asp 1330	Ile Met Gln	His Leu 1335	Lys Ser Lys									
25	Lys Arg 1340	Glu Glu Arg	Trp Met 1345	Arg Ala Ser	Lys Arg 1350	Gln Ser Glu									
30	Lys Glu 1355	Met Glu Glu	Leu His 1360	His Asn Ile	Asp Asp 1365	Leu Leu Gln									
35	Glu Lys 1370	Lys Ser Leu	Glu Cys 1375	Glu Val Glu	Glu Leu 1380	His Arg Thr									
40	Val Gln 1385	Lys Arg Gln	Gln Gln 1390	Lys Asp Phe	Ile Asp 1395	Gly Asn Val									
45	Glu Ser 1400	Leu Met Thr	Glu Leu 1405	Glu Ile Glu	Lys Ser 1410	Leu Lys His									
50	His Glu 1415	Asp Ile Val	Asp Glu 1420	Ile Glu Cys	Ile Glu 1425	Lys Thr Leu									
55	Leu Lys 1430	Arg Arg Ser	Glu Leu 1435	Arg Glu Ala	Asp Arg 1440	Leu Leu Ala									
	Glu Ala 1445	Glu Ser Glu	Leu Ser 1450	Cys Thr Lys	Glu Lys 1455	Thr Lys Asn									
	Ala Val 1460	Glu Lys Phe	Thr Asp 1465	Ala Lys Arg	Ser Leu 1470	Leu Gln Thr									
	Glu Ser 1475	Asp Ala Glu	Glu Leu 1480	Glu Arg Arg	Ala Gln 1485	Glu Thr Ala									
	Val Asn 1490	Leu Val Lys	Ala Asp 1495	Gln Gln Leu	Arg Ser 1500	Leu Gln Ala									

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	Asp	Ala	Lys	Asp	Leu	Glu	Gln	His	Lys	Ile	Lys	Gln	Glu	Glu	Ile
	1505						1510					1515			
5	Leu	Lys	Glu	Ile	Asn	Lys	Ile	Val	Ala	Ala	Lys	Asp	Ser	Asp	Phe
	1520						1525					1530			
10	Gln	Cys	Leu	Ser	Lys	Lys	Lys	Glu	Lys	Leu	Thr	Glu	Glu	Leu	Gln
	1535						1540					1545			
15	Lys	Leu	Gln	Lys	Asp	Ile	Glu	Met	Ala	Glu	Arg	Asn	Glu	Asp	His
	1550						1555					1560			
20	His	Leu	Gln	Val	Leu	Lys	Glu	Ser	Glu	Val	Leu	Leu	Gln	Ala	Lys
	1565						1570					1575			
25	Arg	Ala	Glu	Leu	Glu	Lys	Leu	Lys	Ser	Gln	Val	Thr	Ser	Gln	Gln
	1580						1585					1590			
30	Gln	Glu	Met	Ala	Val	Leu	Asp	Arg	Gln	Leu	Gly	His	Lys	Lys	Glu
	1595						1600					1605			
35	Glu	Leu	His	Leu	Leu	Gln	Gly	Ser	Met	Val	Gln	Ala	Lys	Ala	Asp
	1610						1615					1620			
40	Leu	Gln	Glu	Ala	Leu	Arg	Leu	Gly	Glu	Thr	Glu	Val	Thr	Glu	Lys
	1625						1630					1635			
45	Cys	Asn	His	Ile	Arg	Glu	Val	Lys	Ser	Leu	Leu	Glu	Glu	Leu	Ser
	1640						1645					1650			
50	Phe	Gln	Lys	Gly	Glu	Leu	Asn	Val	Gln	Ile	Ser	Glu	Arg	Lys	Thr
	1655						1660					1665			
55	Gln	Leu	Thr	Leu	Ile	Lys	Gln	Glu	Ile	Glu	Lys	Glu	Glu	Glu	Asn
	1670						1675					1680			
60	Leu	Gln	Val	Val	Leu	Arg	Gln	Met	Ser	Lys	His	Lys	Thr	Glu	Leu
	1685						1690					1695			
65	Lys	Asn	Ile	Leu	Asp	Met	Leu	Gln	Leu	Glu	Asn	His	Glu	Leu	Gln
	1700						1705					1710			
70	Gly	Leu	Lys	Leu	Gln	His	Asp	Gln	Arg	Val	Ser	Glu	Leu	Glu	Lys
	1715						1720					1725			
75	Thr	Gln	Val	Ala	Val	Leu	Glu	Glu	Lys	Leu	Glu	Leu	Glu	Asn	Leu
	1730						1735					1740			

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	Gln	Gln	Ile	Ser	Gln	Gln	Gln	Lys	Gly	Glu	Ile	Glu	Trp	Gln	Lys
	1745						1750					1755			
5	Gln	Leu	Leu	Glu	Arg	Asp	Lys	Arg	Glu	Ile	Glu	Arg	Met	Thr	Ala
	1760						1765					1770			
10	Glu	Ser	Arg	Ala	Leu	Gln	Ser	Cys	Val	Glu	Cys	Leu	Ser	Lys	Glu
	1775						1780					1785			
	Lys	Glu	Asp	Leu	Gln	Glu	Lys	Cys	Asp	Ile	Trp	Glu	Lys	Lys	Leu
	1790						1795					1800			
15	Ala	Gln	Thr	Lys	Arg	Val	Leu	Ala	Ala	Ala	Glu	Glu	Asn	Ser	Lys
	1805						1810					1815			
20	Met	Glu	Gln	Ser	Asn	Leu	Glu	Lys	Leu	Glu	Leu	Asn	Val	Arg	Lys
	1820						1825					1830			
	Leu	Gln	Gln	Glu	Leu	Asp	Gln	Leu	Asn	Arg	Asp	Lys	Leu	Ser	Leu
25	1835						1840					1845			
	His	Asn	Asp	Ile	Ser	Ala	Met	Gln	Gln	Gln	Leu	Gln	Glu	Lys	Arg
	1850						1855					1860			
30	Glu	Ala	Val	Asn	Ser	Leu	Gln	Glu	Glu	Leu	Ala	Asn	Val	Gln	Asp
	1865						1870					1875			
35	His	Leu	Asn	Leu	Ala	Lys	Gln	Asp	Leu	Leu	His	Thr	Thr	Lys	His
	1880						1885					1890			
	Gln	Asp	Val	Leu	Leu	Ser	Glu	Gln	Thr	Arg	Leu	Gln	Lys	Asp	Ile
	1895						1900					1905			
40	Ser	Glu	Trp	Ala	Asn	Arg	Phe	Glu	Asp	Cys	Gln	Lys	Glu	Glu	Glu
	1910						1915					1920			
45	Thr	Lys	Gln	Gln	Gln	Leu	Gln	Val	Leu	Gln	Asn	Glu	Ile	Glu	Glu
	1925						1930					1935			
	Asn	Lys	Leu	Lys	Leu	Val	Gln	Gln	Glu	Met	Met	Phe	Gln	Arg	Leu
50	1940						1945					1950			
	Gln	Lys	Glu	Arg	Glu	Ser	Glu	Glu	Ser	Lys	Leu	Glu	Thr	Ser	Lys
	1955						1960					1965			
55	Val	Thr	Leu	Lys	Glu	Gln	Gln	His	Gln	Leu	Glu	Lys	Glu	Leu	Thr
	1970						1975					1980			

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	Asp	Gln	Lys	Ser	Lys	Leu	Asp	Gln	Val	Leu	Ser	Lys	Val	Leu	Ala
	1985						1990					1995			
5	Ala	Glu	Glu	Arg	Val	Arg	Thr	Leu	Gln	Glu	Glu	Glu	Arg	Trp	Cys
	2000						2005					2010			
10	Glu	Ser	Leu	Glu	Lys	Thr	Leu	Ser	Gln	Thr	Lys	Arg	Gln	Leu	Ser
	2015						2020					2025			
15	Glu	Arg	Glu	Gln	Gln	Leu	Val	Glu	Lys	Ser	Gly	Glu	Leu	Leu	Ala
	2030						2035					2040			
20	Leu	Gln	Lys	Glu	Ala	Asp	Ser	Met	Arg	Ala	Asp	Phe	Ser	Leu	Leu
	2045						2050					2055			
25	Arg	Asn	Gln	Phe	Leu	Thr	Glu	Arg	Lys	Lys	Ala	Glu	Lys	Gln	Val
	2060						2065					2070			
30	Ala	Ser	Leu	Lys	Glu	Ala	Leu	Lys	Ile	Gln	Arg	Ser	Gln	Leu	Glu
	2075						2080					2085			
35	Lys	Asn	Leu	Leu	Glu	Gln	Lys	Gln	Glu	Asn	Ser	Cys	Ile	Gln	Lys
	2090						2095					2100			
40	Glu	Met	Ala	Thr	Ile	Glu	Leu	Val	Ala	Gln	Asp	Asn	His	Glu	Arg
	2105						2110					2115			
45	Ala	Arg	Arg	Leu	Met	Lys	Glu	Leu	Asn	Gln	Met	Gln	Tyr	Glu	Tyr
	2120						2125					2130			
50	Thr	Glu	Leu	Lys	Lys	Gln	Met	Ala	Asn	Gln	Lys	Asp	Leu	Glu	Arg
	2135						2140					2145			
55	Arg	Gln	Met	Glu	Ile	Ser	Asp	Ala	Met	Arg	Thr	Leu	Lys	Ser	Glu
	2150						2155					2160			
60	Val	Lys	Asp	Glu	Ile	Arg	Thr	Ser	Leu	Lys	Asn	Leu	Asn	Gln	Phe
	2165						2170					2175			
65	Leu	Pro	Glu	Leu	Pro	Ala	Asp	Leu	Glu	Ala	Ile	Leu	Glu	Arg	Asn
	2180						2185					2190			
70	Glu	Asn	Leu	Glu	Gly	Glu	Leu	Glu	Ser	Leu	Lys	Glu	Asn	Leu	Pro
	2195						2200					2205			
75	Phe	Thr	Met	Asn	Glu	Gly	Pro	Phe	Glu	Glu	Lys	Leu	Asn	Phe	Ser

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5	Gln Val	His Ile Met Asp	Glu	His Trp Arg Gly	Glu	Ala Leu Arg
	2225		2230		2235	
10	Glu Lys	Leu Arg His Arg	Glu	Asp Arg Leu Lys	Ala	Gln Leu Arg
	2240		2245		2250	
15	His Cys	Met Ser Lys Gln	Ala	Glu Val Leu Ile	Lys	Gly Lys Arg
	2255		2260		2265	
20	Gln Thr	Glu Gly Thr Leu	His	Ser Leu Arg Arg	Gln	Val Asp Ala
	2270		2275		2280	
25	Leu Gly	Glu Leu Val Thr	Ser	Thr Ser Ala Asp	Ser	Ala Ser Ser
	2285		2290		2295	
30	Pro Ser	Leu Ser Gln Leu	Glu	Ser Ser Leu Thr	Glu	Asp Ser Gln
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5	ggg caa gtc gga ggc agc ctg gcc tcc ctc act ggc cag att tca aac	96
	Gly Gln Val Gly Gly Ser Leu Ala Ser Leu Thr Gly Gln Ile Ser Asn	
	20 25 30	
10	ttt acg aag gac atg ctg atg gag ggc acg gag gag gtg gaa gca gaa	144
	Phe Thr Lys Asp Met Leu Met Glu Gly Thr Glu Glu Val Glu Ala Glu	
	35 40 45	
15	tta cct aat tct agg aga aag gaa gtt gaa gcc att cat gca atc tta	192
	Leu Pro Asn Ser Arg Arg Lys Glu Val Glu Ala Ile His Ala Ile Leu	
	50 55 60	
20	aga tca gag aat gag aga ctc aaa gaa ctt tgt act gat tta gaa gag	240
	Arg Ser Glu Asn Glu Arg Leu Lys Glu Leu Cys Thr Asp Leu Glu Glu	
	65 70 75 80	
25	aag cat gaa gca tca gag ctt caa ata aag caa caa tct aca aat tac	288
	Lys His Glu Ala Ser Glu Leu Gln Ile Lys Gln Gln Ser Thr Asn Tyr	
	85 90 95	
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	Arg Asn Gln Leu Gln Gln Lys Glu Val Glu Ile Ser His Leu Lys Ala	
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	Arg Gln Ile Ala Leu Gln Asp Gln Leu Leu Lys Leu Gln Ser Ala Ala	
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	Gln Ser Ala His Ser Gly Ala Ser Ser Val Pro Ala Ala Leu Ala Ser	
	130 135 140	
45	tct ccg ttc agc tat tct gtc agt cat cat gct tca gct ttc cat gac	480
	Ser Pro Phe Ser Tyr Ser Val Ser His His Ala Ser Ala Phe His Asp	
	145 150 155 160	
50	gat gac atg gac ttc agt gac ata att tca tca caa caa gaa ata aac	528
	Asp Asp Met Asp Phe Ser Asp Ile Ile Ser Ser Gln Gln Glu Ile Asn	
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55	aga tta tca aat gaa gtt tca aga ctt gag tct gag gtt ggc cat tgg	576
	Arg Leu Ser Asn Glu Val Ser Arg Leu Glu Ser Glu Val Gly His Trp	
	180 185 190	
60	agg cat att gct cag act tct aaa gca caa gga tca aat agc tct gat	624
	Arg His Ile Ala Gln Thr Ser Lys Ala Gln Gly Ser Asn Ser Ser Asp	
	195 200 205	
65	caa agt gaa atc tgt aaa cta caa agt atc att aag gaa ctc aaa cag	672
	Gln Ser Glu Ile Cys Lys Leu Gln Ser Ile Ile Lys Glu Leu Lys Gln	
	210 215 220	
70	att cga agt cag gaa atc gat gac cat caa cat gaa atg tca gtg ttg	720
	Ile Arg Ser Gln Glu Ile Asp Asp His Gln His Glu Met Ser Val Leu	
	225 230 235 240	
75	cag aat gca cat caa cag aag ttg aca gat ata agt cgt cgg cat cga	768
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[illegible]

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	atc	att	agt	aaa	ctg	aga	aaa	gat	cta	aat	gat	gaa	aac	aag	aga	gtc	1632	
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	545					550					555					560		
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	Gln	Lys	Glu	Lys	Leu	Val	Gln	Ser	Glu	Leu	Val	Leu	Asn	Gly	Leu	His		
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	Leu	Ala	Lys	Gln	Lys	Leu	Glu	Glu	Lys	Val	Glu	Asp	Leu	Val	Asp	Gln		
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	Leu	Asn	Lys	Ser	Gln	Lys	Ser	Asn	Leu	Asn	Met	Gln	Lys	Glu	Asn	Phe		
			595				600						605					
25	gga	ctt	aag	gaa	cat	att	aaa	caa	aat	gag	gaa	gag	ctt	tct	aga	gtc	1872	
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	Gln	Asn	Leu	Ser	Glu	Ile	Glu	Gln	Leu	Asn	Asp	Ser	Leu	Asn	Lys	Val		
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	Ser	Gln	Glu	Lys	Asp	Phe	Glu	Ile	Ala	Glu	Leu	Lys	Lys	Asn	Ile	Glu	
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	Gln	Met	Asp	Thr	Asp	His	Lys	Glu	Thr	Lys	Ala	Ile	Leu	Ser	Ser	Ile	
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	Ile	Lys	Arg	His	Gln	Lys	Ile	Ile	Glu	Asp	Gln	Asn	Gln	Ser	Lys	Met	
			915					920					925				
	cag	ctg	ctt	cag	tct	cta	gag	gag	cag	aag	aag	gaa	atg	gat	gaa	ttt	2832
	Gln	Leu	Leu	Gln	Ser	Leu	Glu	Glu	Gln	Lys	Lys	Glu	Met	Asp	Glu	Phe	
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	Lys	Cys	Gln	His	Glu	Gln	Met	Asn	Val	Thr	His	Thr	Gln	Leu	Phe	Leu	
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	Glu	Lys	Asp	Glu	Glu	Ile	Lys	Asn	Leu	Gln	Lys	Thr	Ile	Glu	Gln	Ile	
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	Lys	Thr	Gln	Trp	His	Glu	Glu	Arg	Gln	Asp	Val	Gln	Met	Glu	Asn	Ser	
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	Glu	Phe	Phe	Gln	Glu	Thr	Lys	Val	Gln	Ser	Leu	Asn	Leu	Glu	Asn	Gly	
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	agt gaa aag cat gat tta tcg aaa gcc gaa act gag agg tta gta Ser Glu Lys His Asp Leu Ser Lys Ala Glu Thr Glu Arg Leu Val 1010 1015 1020	3069
5	aaa gga ata aaa gaa cga gag ctg gag att aaa ctt cta aat gaa Lys Gly Ile Lys Glu Arg Glu Leu Glu Ile Lys Leu Leu Asn Glu 1025 1030 1035	3114
10	aag aat ata tct tta aca aaa caa att gat cag ctg tcc aaa gat Lys Asn Ile Ser Leu Thr Lys Gln Ile Asp Gln Leu Ser Lys Asp 1040 1045 1050	3159
15	gag gtt ggt aaa ctc act cag atc atc cag cag aaa gac tta gag Glu Val Gly Lys Leu Thr Gln Ile Ile Gln Gln Lys Asp Leu Glu 1055 1060 1065	3204
20	ata caa gct ctt cat gct agg att tct tca gct tcc tac acc cag Ile Gln Ala Leu His Ala Arg Ile Ser Ser Ala Ser Tyr Thr Gln 1070 1075 1080	3249
25	gat gtt gtc tac ctt cag cag cag ctg cag gcc tat gct atg gag Asp Val Val Tyr Leu Gln Gln Gln Leu Gln Ala Tyr Ala Met Glu 1085 1090 1095	3294
30	aga gaa caa gta tta gct gtt ttg agt gag aag acc agg gaa aat Arg Glu Gln Val Leu Ala Val Leu Ser Glu Lys Thr Arg Glu Asn 1100 1105 1110	3339
35	agc cat ctg aaa aca gaa tac cac aaa atg atg gat atc gtt gct Ser His Leu Lys Thr Glu Tyr His Lys Met Met Asp Ile Val Ala 1115 1120 1125	3384
40	gct aaa gaa gca gct ctc att aag ctg caa gat gaa aat aaa aaa Ala Lys Glu Ala Ala Leu Ile Lys Leu Gln Asp Glu Asn Lys Lys 1130 1135 1140	3429
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	cag ctt cag gca caa gtt ttg gtt gac agt gat aat aat tct aaa 3789 Gln Leu Gln Ala Gln Val Leu Val Asp Ser Asp Asn Asn Ser Lys 1250 1255 1260
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15	cac agc ata ggg cag ctg tac agt acc aaa gac ctt ctc tta gga 3924 His Ser Ile Gly Gln Leu Tyr Ser Thr Lys Asp Leu Leu Leu Gly 1295 1300 1305
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		1475					1480					1485					
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		1610															
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		1625															
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		1640															
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		1655															
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		1685															
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		1700															
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	1880						1885					1890				
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	Arg	Ser	Ala	Ala	Val	Pro	Leu	Ile	Asn	Pro	Ala	Gly	Leu	Gly	Pro	
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1955 1960 1965

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1970 1975

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35 40 45

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50 55 60

35 Arg Ser Glu Asn Glu Arg Leu Lys Glu Leu Cys Thr Asp Leu Glu Glu
65 70 75 80

Lys His Glu Ala Ser Glu Leu Gln Ile Lys Gln Gln Ser Thr Asn Tyr
85 90 95

40 Arg Asn Gln Leu Gln Gln Lys Glu Val Glu Ile Ser His Leu Lys Ala
100 105 110

45 Arg Gln Ile Ala Leu Gln Asp Gln Leu Leu Lys Leu Gln Ser Ala Ala
115 120 125

Gln Ser Ala His Ser Gly Ala Ser Ser Val Pro Ala Ala Leu Ala Ser
130 135 140

50 Ser Pro Phe Ser Tyr Ser Val Ser His His Ala Ser Ala Phe His Asp
145 150 155 160

55 Asp Asp Met Asp Phe Ser Asp Ile Ile Ser Ser Gln Gln Glu Ile Asn
165 170 175

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	Arg	Leu	Ser	Asn	Glu	Val	Ser	Arg	Leu	Glu	Ser	Glu	Val	Gly	His	Trp	180	185	190	
5	Arg	His	Ile	Ala	Gln	Thr	Ser	Lys	Ala	Gln	Gly	Ser	Asn	Ser	Ser	Asp	195	200	205	
10	Gln	Ser	Glu	Ile	Cys	Lys	Leu	Gln	Ser	Ile	Ile	Lys	Glu	Leu	Lys	Gln	210	215	220	
	Ile	Arg	Ser	Gln	Glu	Ile	Asp	Asp	His	Gln	His	Glu	Met	Ser	Val	Leu	225	230	235	240
15	Gln	Asn	Ala	His	Gln	Gln	Lys	Leu	Thr	Asp	Ile	Ser	Arg	Arg	His	Arg	245	250	255	
20	Glu	Glu	Leu	Arg	Asp	Tyr	Glu	Glu	Arg	Ile	Glu	Glu	Leu	Glu	Asn	Leu	260	265	270	
25	Leu	Glu	Gln	Gly	Gly	Ser	Gly	Ile	Val	Ile	Pro	Asp	His	Ser	Lys	Ile	275	280	285	
	His	Glu	Met	Gln	Lys	Thr	Ile	Gln	Asn	Leu	Gln	Thr	Glu	Lys	Val	Ala	290	295	300	
30	Ser	Ile	Lys	Lys	Ile	Glu	Glu	Leu	Glu	Asp	Lys	Ile	Lys	Asp	Ile	Asp	305	310	315	320
35	Lys	Lys	Leu	Ser	Ser	Ala	Glu	Asn	Asp	Arg	Asp	Val	Leu	Arg	Lys	Glu	325	330	335	
40	Lys	Glu	Cys	Leu	Asn	Val	Glu	Asn	Arg	Gln	Ile	Thr	Glu	Gln	Cys	Glu	340	345	350	
	Ser	Leu	Lys	Leu	Glu	Cys	Lys	Leu	Gln	His	Asp	Ala	Glu	Lys	Gln	Gly	355	360	365	
45	Asp	Thr	Val	Thr	Glu	Lys	Glu	Arg	Ile	Leu	Pro	Gln	Ser	Thr	Ser	Val	370	375	380	
50	Glu	Glu	Glu	Val	Leu	Lys	Leu	Gln	Gln	Ala	Leu	Ser	Asp	Ala	Glu	Asn	385	390	395	400
	Glu	Ile	Met	Arg	Leu	Ser	Asn	Leu	Tyr	Gln	Asp	Asn	Ser	Leu	Thr	Glu	405	410	415	
55	Asp	Asn	Leu	Lys	Leu	Lys	Met	His	Val	Glu	Phe	Leu	Glu	Lys	Gln	Lys	420	425	430	

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	Ser	Leu	Leu	Ser	Gln	Glu	Lys	Glu	Glu	Leu	Gln	Leu	Ser	Leu	Leu	Lys	
				435				440					445				
5	Leu	Asn	Asn	Glu	Tyr	Glu	Val	Ile	Lys	Ser	Thr	Ala	Val	Arg	Asp	Met	
		450					455					460					
10	Asp	Met	Asp	Ser	Thr	Leu	Cys	Asp	Leu	Arg	Leu	Thr	Leu	Glu	Ala	Lys	
	465					470					475					480	
15	Asp	Gln	Glu	Leu	Asn	Gln	Ser	Leu	Thr	Glu	Lys	Glu	Ile	Leu	Val	Ala	
					485					490					495		
20	Glu	Leu	Glu	Glu	Leu	Asp	Arg	Gln	Asn	Gln	Glu	Ala	Thr	Lys	His	Met	
				500					505					510			
25	Ile	Leu	Ile	Lys	Asp	Gln	Leu	Ser	Lys	Gln	Gln	Ser	Glu	Gly	Glu	Thr	
			515					520					525				
30	Ile	Ile	Ser	Lys	Leu	Arg	Lys	Asp	Leu	Asn	Asp	Glu	Asn	Lys	Arg	Val	
		530					535					540					
35	His	Gln	Leu	Glu	Asp	Asp	Lys	Lys	Asn	Met	Thr	Lys	Glu	Leu	Asn	Val	
	545					550					555					560	
40	Gln	Lys	Glu	Lys	Leu	Val	Gln	Ser	Glu	Leu	Val	Leu	Asn	Gly	Leu	His	
					565					570					575		
45	Leu	Ala	Lys	Gln	Lys	Leu	Glu	Glu	Lys	Val	Glu	Asp	Leu	Val	Asp	Gln	
				580					585					590			
50	Leu	Asn	Lys	Ser	Gln	Lys	Ser	Asn	Leu	Asn	Met	Gln	Lys	Glu	Asn	Phe	
			595					600					605				
55	Gly	Leu	Lys	Glu	His	Ile	Lys	Gln	Asn	Glu	Glu	Glu	Leu	Ser	Arg	Val	
		610					615					620					
60	Arg	Asp	Glu	Leu	Thr	Gln	Ser	Leu	Ser	Arg	Asp	Ser	Gly	Ser	Asp	Phe	
	625					630					635					640	
65	Lys	Asp	Asp	Leu	Leu	Lys	Glu	Arg	Glu	Ala	Glu	Val	Arg	Asn	Leu	Lys	
					645					650					655		
70	Gln	Asn	Leu	Ser	Glu	Ile	Glu	Gln	Leu	Asn	Asp	Ser	Leu	Asn	Lys	Val	
				660					665					670			
75	Ala	Phe	Asp	Leu	Lys	Met	Glu	Asn	Glu	Lys	Leu	Val	Leu	Ala	Cys	Glu	

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	675					680					685					
5	Asp	Ile	Arg	His	Gln	Leu	Glu	Glu	Ser	Ile	Val	Gly	Ser	Asn	Gln	Met
	690						695					700				
10	Ser	Leu	Glu	Arg	Asn	Thr	Ile	Val	Glu	Ala	Leu	Lys	Met	Glu	Lys	Gly
	705					710					715					720
15	Gln	Leu	Glu	Ala	Glu	Leu	Ser	Arg	Ala	Asp	Gln	Arg	Leu	Leu	Glu	Glu
					725					730					735	
20	Ala	Ser	Lys	Tyr	Glu	Gln	Thr	Ile	Gln	Glu	Leu	Ser	Lys	Ala	Arg	Asp
				740					745					750		
25	Leu	Arg	Thr	Ser	Ala	Leu	Gln	Leu	Glu	Gln	Gln	His	Leu	Met	Lys	Leu
			755					760					765			
30	Ser	Gln	Glu	Lys	Asp	Phe	Glu	Ile	Ala	Glu	Leu	Lys	Lys	Asn	Ile	Glu
	770						775					780				
35	Gln	Met	Asp	Thr	Asp	His	Lys	Glu	Thr	Lys	Ala	Ile	Leu	Ser	Ser	Ile
	785					790					795					800
40	Leu	Glu	Glu	Gln	Lys	Gln	Leu	Thr	Gln	Leu	Ile	Ser	Glu	Lys	Glu	Ile
					805					810					815	
45	Phe	Ile	Glu	Lys	Leu	Lys	Glu	Arg	Ser	Ser	Glu	Leu	Gln	Glu	Glu	Leu
				820					825					830		
50	Glu	Lys	Ser	Thr	Gln	Ala	Ser	Arg	Lys	Ile	Glu	Ile	Leu	Lys	Gln	Thr
			835					840					845			
55	Ile	Glu	Glu	Lys	Asp	Arg	Ser	Leu	Gly	Ser	Met	Lys	Glu	Glu	Asn	Asn
	850						855					860				
60	His	Leu	Lys	Glu	Glu	Leu	Glu	Arg	Leu	Arg	Glu	Gln	Gln	Ser	Arg	Ala
	865					870					875					880
65	Val	Pro	Val	Val	Glu	Pro	Lys	Pro	Leu	Asp	Ser	Val	Thr	Glu	Leu	Glu
					885					890					895	
70	Ser	Glu	Val	Leu	Gln	Leu	Asn	Ile	Val	Lys	Arg	Asn	Leu	Glu	Glu	Glu
				900					905					910		
75	Ile	Lys	Arg	His	Gln	Lys	Ile	Ile	Glu	Asp	Gln	Asn	Gln	Ser	Lys	Met
			915					920					925			

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	Gln	Leu	Leu	Gln	Ser	Leu	Glu	Glu	Gln	Lys	Lys	Glu	Met	Asp	Glu	Phe	
	930						935					940					
5	Lys	Cys	Gln	His	Glu	Gln	Met	Asn	Val	Thr	His	Thr	Gln	Leu	Phe	Leu	
	945					950					955					960	
	Glu	Lys	Asp	Glu	Glu	Ile	Lys	Asn	Leu	Gln	Lys	Thr	Ile	Glu	Gln	Ile	
10					965					970					975		
	Lys	Thr	Gln	Trp	His	Glu	Glu	Arg	Gln	Asp	Val	Gln	Met	Glu	Asn	Ser	
				980					985					990			
15	Glu	Phe	Phe	Gln	Glu	Thr	Lys	Val	Gln	Ser	Leu	Asn	Leu	Glu	Asn	Gly	
			995					1000					1005				
	Ser	Glu	Lys	His	Asp	Leu	Ser	Lys	Ala	Glu	Thr	Glu	Arg	Leu	Val		
20		1010					1015					1020					
	Lys	Gly	Ile	Lys	Glu	Arg	Glu	Leu	Glu	Ile	Lys	Leu	Leu	Asn	Glu		
25		1025					1030					1035					
	Lys	Asn	Ile	Ser	Leu	Thr	Lys	Gln	Ile	Asp	Gln	Leu	Ser	Lys	Asp		
		1040					1045					1050					
30	Glu	Val	Gly	Lys	Leu	Thr	Gln	Ile	Ile	Gln	Gln	Lys	Asp	Leu	Glu		
		1055					1060					1065					
	Ile	Gln	Ala	Leu	His	Ala	Arg	Ile	Ser	Ser	Ala	Ser	Tyr	Thr	Gln		
35		1070					1075					1080					
	Asp	Val	Val	Tyr	Leu	Gln	Gln	Gln	Leu	Gln	Ala	Tyr	Ala	Met	Glu		
		1085					1090					1095					
40	Arg	Glu	Gln	Val	Leu	Ala	Val	Leu	Ser	Glu	Lys	Thr	Arg	Glu	Asn		
		1100					1105					1110					
	Ser	His	Leu	Lys	Thr	Glu	Tyr	His	Lys	Met	Met	Asp	Ile	Val	Ala		
45		1115					1120					1125					
	Ala	Lys	Glu	Ala	Ala	Leu	Ile	Lys	Leu	Gln	Asp	Glu	Asn	Lys	Lys		
50		1130					1135					1140					
	Leu	Ser	Ala	Arg	Ser	Glu	Gly	Gly	Gly	Gln	Asp	Met	Phe	Arg	Glu		
		1145					1150					1155					
55	Thr	Val	Gln	Asn	Leu	Ser	Arg	Ile	Ile	Arg	Glu	Lys	Asp	Ile	Glu		
		1160					1165					1170					

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	Ile Asp	Ala Leu Ser Gln Lys	Cys Gln Thr Leu Leu	Thr Val Leu
	1175	1180	1185	
5	Gln Thr	Ser Ser Thr Gly Asn	Glu Val Gly Gly Val	Asn Ser Asn
	1190	1195	1200	
10	Gln Phe	Glu Glu Leu Leu Gln	Glu Arg Asp Lys Leu	Lys Gln Gln
	1205	1210	1215	
	Val Lys	Lys Met Glu Glu Trp	Lys Gln Gln Val Met	Thr Thr Val
	1220	1225	1230	
15	Gln Asn	Met Gln His Glu Ser	Ala Gln Leu Gln Glu	Glu Leu His
	1235	1240	1245	
20	Gln Leu	Gln Ala Gln Val Leu	Val Asp Ser Asp Asn	Asn Ser Lys
	1250	1255	1260	
	Leu Gln	Val Asp Tyr Thr Gly	Leu Ile Gln Ser Tyr	Glu Gln Asn
	1265	1270	1275	
25	Glu Thr	Lys Leu Lys Asn Phe	Gly Gln Glu Leu Ala	Gln Val Gln
	1280	1285	1290	
30	His Ser	Ile Gly Gln Leu Tyr	Ser Thr Lys Asp Leu	Leu Leu Gly
	1295	1300	1305	
35	Lys Leu	Asp Ile Ile Ser Pro	Gln Leu Pro Ser Gly	Ser Ser Pro
	1310	1315	1320	
	Pro Ser	Gln Ser Ala Glu Ser	Leu Gly Met Asp Lys	Arg Asp Thr
	1325	1330	1335	
40	Ser Ser	Glu Ser Ser Lys Gln	Glu Leu Glu Glu Leu	Arg Lys Ser
	1340	1345	1350	
45	Leu Gln	Glu Lys Asp Ala Thr	Ile Lys Thr Leu Gln	Glu Asn Asn
	1355	1360	1365	
	His Arg	Leu Ser Asp Ser Ile	Ala Ala Thr Ser Glu	Leu Glu Arg
	1370	1375	1380	
50	Lys Glu	His Glu Gln Thr Asp	Ser Glu Ile Lys Gln	Leu Lys Glu
	1385	1390	1395	
55	Lys Gln	Asp Val Leu Gln Lys	Ser Leu Lys Glu Lys	Asp Leu Leu
	1400	1405	1410	

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	Ile Lys	Ala Lys	Ser Asp	Gln	Leu Leu	Ser Leu	Asn	Glu Asn	Phe
	1415			1420			1425		
5	Thr Asn	Lys Val	Asn Glu	Asn	Glu Leu	Leu Arg	Gln	Ala Val	Thr
	1430			1435			1440		
10	Asn Leu	Lys Glu	Arg Val	Leu	Ile Leu	Glu Met	Asp	Ile Gly	Lys
	1445			1450			1455		
15	Leu Lys	Glu Glu	Asn Glu	Lys	Ile Val	Glu Arg	Thr	Arg Glu	Lys
	1460			1465			1470		
20	Glu Thr	Glu Tyr	Gln Ala	Leu	Gln Glu	Thr Asn	Met	Lys Phe	Ser
	1475			1480			1485		
25	Met Met	Leu Arg	Glu Lys	Glu	Phe Glu	Cys His	Ser	Met Lys	Glu
	1490			1495			1500		
30	Lys Ser	Leu Ala	Phe Glu	Gln	Leu Leu	Lys Glu	Lys	Glu Gln	Gly
	1505			1510			1515		
35	Lys Thr	Gly Glu	Leu Asn	Gln	Leu Leu	Asn Ala	Val	Lys Ser	Met
	1520			1525			1530		
40	Gln Glu	Lys Thr	Val Lys	Phe	Gln Gln	Glu Arg	Asp	Gln Val	Met
	1535			1540			1545		
45	Leu Ala	Leu Lys	Gln Lys	Gln	Met Glu	Asn Ser	Ala	Leu Gln	Asn
	1550			1555			1560		
50	Glu Val	Gln His	Leu Arg	Asp	Lys Glu	Leu Arg	Leu	Asn Gln	Glu
	1565			1570			1575		
55	Leu Glu	Arg Leu	Arg Asn	His	Leu Leu	Glu Ser	Glu	Asp Ser	Tyr
	1580			1585			1590		
	Thr Arg	Glu Ala	Leu Ala	Ala	Glu Glu	Arg Glu	Ala	Lys Leu	Arg
	1595			1600			1605		
	Arg Lys	Val Thr	Val Leu	Glu	Glu Lys	Leu Val	Ser	Ser Ser	Asn
	1610			1615			1620		
	Ala Met	Glu Asn	Ala Ser	His	Gln Ala	Ser Leu	Gln	Val Glu	Ser
	1625			1630			1635		
	Leu Gln	Glu Gln	Leu Asn	Val	Val Ser	Lys Gln	Arg	Asp Glu	Thr

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[illegible]

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	Leu	Ser	Val	His	Asp	Met	Lys	Pro	Leu	Asp	Ser	Pro	Gly	Arg	Arg	
	1880						1885					1890				
5	Lys	Val	Val	Ile	His	Val	Ser	Glu	Ser	Phe	Lys	Glu	Thr	Thr	Glu	
	1895						1900					1905				
10	Ser	Arg	Cys	Gly	Arg	Arg	Thr	Asp	Val	Asn	Pro	Phe	Leu	Ala	Pro	
	1910						1915					1920				
15	Arg	Ser	Ala	Ala	Val	Pro	Leu	Ile	Asn	Pro	Ala	Gly	Leu	Gly	Pro	
	1925						1930					1935				
20	Gly	Gly	Pro	Gly	His	Leu	Leu	Leu	Lys	Pro	Ile	Ser	Asp	Val	Leu	
	1940						1945					1950				
25	Pro	Thr	Phe	Thr	Pro	Leu	Pro	Val	Ser	Pro	Asp	Asn	Ser	Ala	Gly	
	1955						1960					1965				
30	Val	Val	Leu	Lys	Asp	Leu	Leu	Lys	Gln							
	1970						1975									
35	<210>	40														
	<211>	6452														
	<212>	DNA														
	<213>	Homo sapiens														
40	<220>															
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	<222>	(357) .. (6296)														
	<223>															
45	<400>	40														
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	agtcattaga	gctgagaaag	aagtggccca	atctggacgg	tgggaattcg	tgggaatgag										120
50	cagaaggccc	tccgtagtga	ctgtgtcact	agaggcgggc	ccctggtaaa	attccaggcc										180
	aggcctctgc	gtttctaggc	agaacctgga	gtcggccttg	cctgagaacc	cagctttgtg										240
	ttatcgtatc	ctgtctcgcg	aaggcaggcg	ttcaaggata	tttggtcggg	tcgcccggcg										300
55	gcgctaaaacg	ttttcttttt	tccgagcggg	ccgggtcggt	ctctaaactc	gccgcg atg										359
						Met										1
	tcg tcc tgg ctt ggg ggc ctc ggc tcc gga ttg ggc cag tct ctg ggt															407
60	Ser Ser Trp Leu Gly Gly Leu Gly Ser Gly Leu Gly Gln Ser Leu Gly															
		5						10					15			
	caa gtc ggg ggc agc ctg gct tcc ctc act ggc cag ata tca aac ttt															455
	Gln Val Gly Gly Ser Leu Ala Ser Leu Thr Gly Gln Ile Ser Asn Phe															
		20						25					30			
65	aca aag gat atg ctg atg gag ggc acg gag gaa gtg gaa gca gaa tta															503
	Thr Lys Asp Met Leu Met Glu Gly Thr Glu Glu Val Glu Ala Glu Leu															

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	35	40	45	
5	cct gat tct agg aca aag gaa att gaa gcc att cat gca atc ttg aga Pro Asp Ser Arg Thr Lys Glu Ile Glu Ala Ile His Ala Ile Leu Arg 50 55 60 65	551		
10	tca gag aat gaa agg ctt aag aaa ctt tgt act gat cta gaa gag aaa Ser Glu Asn Glu Arg Leu Lys Lys Leu Cys Thr Asp Leu Glu Glu Lys 70 75 80	599		
15	cat gaa gca tca gag att caa ata aag cag caa tct aca agt tac cga His Glu Ala Ser Glu Ile Gln Ile Lys Gln Gln Ser Thr Ser Tyr Arg 85 90 95	647		
20	aat caa ctt caa caa aaa gag gta gaa atc agc cat ctt aaa gcc aga Asn Gln Leu Gln Gln Lys Glu Val Glu Ile Ser His Leu Lys Ala Arg 100 105 110	695		
25	cag att gca ctc cag gat cag ttg ctg aaa ctg cag tca gct gct cag Gln Ile Ala Leu Gln Asp Gln Leu Leu Lys Leu Gln Ser Ala Ala Gln 115 120 125	743		
30	tca gta cct tca gga gct ggt gta cca gca acc act gca tca tct tca Ser Val Pro Ser Gly Ala Gly Val Pro Ala Thr Thr Ala Ser Ser Ser 130 135 140 145	791		
35	ttc gct tat ggg att agt cat cat cct tca gct ttc cat gac gat gac Phe Ala Tyr Gly Ile Ser His His Pro Ser Ala Phe His Asp Asp Asp 150 155 160	839		
40	atg gac ttt ggt gat ata att tca tcc caa caa gaa ata aac cga ctc Met Asp Phe Gly Asp Ile Ile Ser Ser Gln Gln Glu Ile Asn Arg Leu 165 170 175	887		
45	tca aat gaa gtt tca aga ctt gag tct gaa gtt ggc cat tgg agg cat Ser Asn Glu Val Ser Arg Leu Glu Ser Glu Val Gly His Trp Arg His 180 185 190	935		
50	att gct cag act tcc aaa gca caa gga aca gat aac tct gat caa agt Ile Ala Gln Thr Ser Lys Ala Gln Gly Thr Asp Asn Ser Asp Gln Ser 195 200 205	983		
55	gaa ata tgt aaa cta caa aat atc att aag gaa cta aaa cag aac cga Glu Ile Cys Lys Leu Gln Asn Ile Ile Lys Glu Leu Lys Gln Asn Arg 210 215 220 225	1031		
60	agt cag gaa att gat gac cat caa cat gaa atg tca gta ctg cag aat Ser Gln Glu Ile Asp Asp His Gln His Glu Met Ser Val Leu Gln Asn 230 235 240	1079		
65	gca cac caa cag aaa ttg aca gaa ata agt cga cga cat cga gaa gaa Ala His Gln Gln Lys Leu Thr Glu Ile Ser Arg Arg His Arg Glu Glu 245 250 255	1127		
70	tta agt gac tat gaa gaa cga att gaa gaa ctt gaa aat ctg tta caa Leu Ser Asp Tyr Glu Glu Arg Ile Glu Glu Leu Glu Asn Leu Leu Gln 260 265 270	1175		
75	caa ggt ggc tct gga gtt ata gaa act gat ctc tct aaa atc tat gag Gln Gly Gly Ser Gly Val Ile Glu Thr Asp Leu Ser Lys Ile Tyr Glu 275 280 285	1223		
80	atg caa aaa act att caa gtt cta caa ata gaa aaa gtg gag tct acc	1271		

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	Met	Gln	Lys	Thr	Ile	Gln	Val	Leu	Gln	Ile	Glu	Lys	Val	Glu	Ser	Thr	
	290					295					300					305	
5	aaa	aaa	atg	gaa	caa	ctt	gag	gat	aaa	ata	aaa	gat	ata	aat	aaa	aaa	1319
	Lys	Lys	Met	Glu	Gln	Leu	Glu	Asp	Lys	Ile	Lys	Asp	Ile	Asn	Lys	Lys	
					310					315					320		
10	tta	tct	tct	gca	gaa	aat	gac	aga	gat	att	ttg	agg	agg	gaa	caa	gaa	1367
	Leu	Ser	Ser	Ala	Glu	Asn	Asp	Arg	Asp	Ile	Leu	Arg	Arg	Glu	Gln	Glu	
				325					330					335			
	cag	cta	aat	gtg	gaa	aag	aga	caa	ata	atg	gaa	gaa	tgt	gaa	aac	ttg	1415
	Gln	Leu	Asn	Val	Glu	Lys	Arg	Gln	Ile	Met	Glu	Glu	Cys	Glu	Asn	Leu	
			340					345					350				
15	aaa	ttg	gaa	tgt	agt	aaa	ttg	cag	cct	tct	gct	gtg	aag	caa	agt	gat	1463
	Lys	Leu	Glu	Cys	Ser	Lys	Leu	Gln	Pro	Ser	Ala	Val	Lys	Gln	Ser	Asp	
		355					360					365					
20	act	atg	aca	gaa	aag	gaa	aga	att	ctt	gcc	cag	agt	gca	tca	gtg	gaa	1511
	Thr	Met	Thr	Glu	Lys	Glu	Arg	Ile	Leu	Ala	Gln	Ser	Ala	Ser	Val	Glu	
	370					375					380					385	
25	gaa	gtg	ttc	aga	cta	caa	caa	gca	ctg	tct	gat	gcc	gaa	aat	gaa	ata	1559
	Glu	Val	Phe	Arg	Leu	Gln	Gln	Ala	Leu	Ser	Asp	Ala	Glu	Asn	Glu	Ile	
					390					395					400		
	atg	aga	ttg	agt	agt	tta	aac	cag	gat	aac	agt	ctt	gct	gaa	gac	aat	1607
	Met	Arg	Leu	Ser	Ser	Leu	Asn	Gln	Asp	Asn	Ser	Leu	Ala	Glu	Asp	Asn	
				405					410					415			
30	ctg	aaa	ctt	aaa	atg	cgt	atc	gaa	gtt	tta	gaa	aaa	gag	aag	tca	tta	1655
	Leu	Lys	Leu	Lys	Met	Arg	Ile	Glu	Val	Leu	Glu	Lys	Glu	Lys	Ser	Leu	
			420					425					430				
35	ctg	agt	caa	gaa	aag	gaa	gaa	ctt	cag	atg	tca	ctt	tta	aaa	ttg	aac	1703
	Leu	Ser	Gln	Glu	Lys	Glu	Glu	Leu	Gln	Met	Ser	Leu	Leu	Lys	Leu	Asn	
		435					440					445					
40	aat	gaa	tat	gaa	gta	att	aaa	agt	aca	gct	aca	aga	gac	ata	agt	ttg	1751
	Asn	Glu	Tyr	Glu	Val	Ile	Lys	Ser	Thr	Ala	Thr	Arg	Asp	Ile	Ser	Leu	
	450					455					460					465	
	gat	tca	gaa	tta	cat	gac	tta	aga	ctt	aat	ttg	gag	gca	aag	gaa	caa	1799
	Asp	Ser	Glu	Leu	His	Asp	Leu	Arg	Leu	Asn	Leu	Glu	Ala	Lys	Glu	Gln	
					470					475					480		
45	gaa	ctc	aat	cag	agt	att	agt	gaa	aag	gaa	aca	ctg	ata	gct	gag	ata	1847
	Glu	Leu	Asn	Gln	Ser	Ile	Ser	Glu	Lys	Glu	Thr	Leu	Ile	Ala	Glu	Ile	
				485					490					495			
50	gaa	gaa	ttg	gac	aga	cag	aat	caa	gaa	gct	aca	aag	cac	atg	att	ttg	1895
	Glu	Glu	Leu	Asp	Arg	Gln	Asn	Gln	Glu	Ala	Thr	Lys	His	Met	Ile	Leu	
			500					505					510				
	ata	aaa	gat	cag	cta	tca	aaa	caa	caa	aat	gaa	gga	gat	agc	atc	atc	1943
	Ile	Lys	Asp	Gln	Leu	Ser	Lys	Gln	Gln	Asn	Glu	Gly	Asp	Ser	Ile	Ile	
		515					520					525					
55	agt	aaa	ctg	aaa	caa	gat	cta	aat	gat	gaa	aaa	aag	aga	gtt	cat	caa	1991
	Ser	Lys	Leu	Lys	Gln	Asp	Leu	Asn	Asp	Glu	Lys	Lys	Arg	Val	His	Gln	
	530					535					540					545	

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	ctt gaa gat gat aaa atg gac att act aaa gag tta gat gta cag aaa	2039
	Leu Glu Asp Asp Lys Met Asp Ile Thr Lys Glu Leu Asp Val Gln Lys	
	550 555 560	
5	gaa aag cta att caa agt gaa gtg gcc cta aat gat tta cat tta acc	2087
	Glu Lys Leu Ile Gln Ser Glu Val Ala Leu Asn Asp Leu His Leu Thr	
	565 570 575	
10	aag cag aaa ctt gag gac aaa gta gaa aat tta gta gat cag cta aat	2135
	Lys Gln Lys Leu Glu Asp Lys Val Glu Asn Leu Val Asp Gln Leu Asn	
	580 585 590	
15	aaa tca caa gaa agt aat gta agc atc cag aag gag aat tta gaa ctt	2183
	Lys Ser Gln Glu Ser Asn Val Ser Ile Gln Lys Glu Asn Leu Glu Leu	
	595 600 605	
20	aag gag cat att aga caa aat gag gag gag ctt tct aga ata agg aat	2231
	Lys Glu His Ile Arg Gln Asn Glu Glu Glu Leu Ser Arg Ile Arg Asn	
	610 615 620 625	
25	gag tta atg cag tct cta aat caa gac tct aat agt aat ttt aag gat	2279
	Glu Leu Met Gln Ser Leu Asn Gln Asp Ser Asn Ser Asn Phe Lys Asp	
	630 635 640	
30	acc tta ctt aaa gaa aga gaa gct gaa gtt aga aac tta aag caa aat	2327
	Thr Leu Leu Lys Glu Arg Glu Ala Glu Val Arg Asn Leu Lys Gln Asn	
	645 650 655	
35	ctt tca gaa tta gaa cag ctc aat gaa aat tta aag aaa gtt gct ttt	2375
	Leu Ser Glu Leu Glu Gln Leu Asn Glu Asn Leu Lys Lys Val Ala Phe	
	660 665 670	
40	gat gtc aaa atg gaa aat gaa aag tta gtt tta gca tgt gaa gat gtg	2423
	Asp Val Lys Met Glu Asn Glu Lys Leu Val Leu Ala Cys Glu Asp Val	
	675 680 685	
45	agg cat cag tta gaa gaa tgt ctt gct ggt aac aat cag ctt tct ctg	2471
	Arg His Gln Leu Glu Glu Cys Leu Ala Gly Asn Asn Gln Leu Ser Leu	
	690 695 700 705	
50	gaa aaa aac act att gtg gag act cta aaa atg gaa aaa gga gag ata	2519
	Glu Lys Asn Thr Ile Val Glu Thr Leu Lys Met Glu Lys Gly Glu Ile	
	710 715 720	
55	gag gca gaa ttg tgt tgg gct aaa aag agg ctg ttg gaa gaa gca aac	2567
	Glu Ala Glu Leu Cys Trp Ala Lys Lys Arg Leu Leu Glu Glu Ala Asn	
	725 730 735	
60	aag tat gag aaa acc att gaa gaa ctg tca aat gca cgt aat ttg aat	2615
	Lys Tyr Glu Lys Thr Ile Glu Glu Leu Ser Asn Ala Arg Asn Leu Asn	
	740 745 750	
65	acc tct gcc tta cag ctg gaa cat gag cat tta att aaa ctc aat caa	2663
	Thr Ser Ala Leu Gln Leu Glu His Glu His Leu Ile Lys Leu Asn Gln	
	755 760 765	
70	aag aaa gac atg gaa ata gca gaa ctc aaa aag aat att gaa caa atg	2711
	Lys Lys Asp Met Glu Ile Ala Glu Leu Lys Lys Asn Ile Glu Gln Met	
	770 775 780 785	
75	gat act gac cat aaa gaa act aag gac gtt ttg tca tct agt tta gaa	2759
	Asp Thr Asp His Lys Glu Thr Lys Asp Val Leu Ser Ser Ser Leu Glu	
	790 795 800	

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[illegible]

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	Lys 1280	Leu	Lys	Asn	Phe	Gly 1285	Gln	Glu	Leu	Ala	Gln 1290	Val	Gln	His	Ser	
5	att Ile 1295	ggg Gly	cag Gln	ctt Leu	tgc Cys	aat Asn 1300	acc Thr	aag Lys	gat Asp	ctt Leu	ctt Leu 1305	tta Leu	gga Gly	aaa Lys	ctt Leu	4283
10	gat Asp 1310	att Ile	att Ile	tca Ser	ccc Pro	cag Gln 1315	ctg Leu	tct Ser	tct Ser	gca Ala	tca Ser 1320	ttg Leu	ctt Leu	act Thr	ccc Pro	4328
	cag Gln 1325	tct Ser	gca Ala	gag Glu	tgt Cys	ctt Leu 1330	aga Arg	gca Ala	agt Ser	aag Lys	tct Ser 1335	gaa Glu	gta Val	ttg Leu	agt Ser	4373
15	gaa Glu 1340	tct Ser	tct Ser	gaa Glu	ttg Leu	ctt Leu 1345	cag Gln	caa Gln	gag Glu	tta Leu	gaa Glu 1350	gag Glu	cta Leu	aga Arg	aaa Lys	4418
20	tca Ser 1355	cta Leu	cag Gln	gaa Glu	aaa Lys	gat Asp 1360	gca Ala	aca Thr	att Ile	aga Arg	act Thr 1365	ctc Leu	cag Gln	gaa Glu	aat Asn	4463
25	aac Asn 1370	cac His	aga Arg	ttg Leu	tct Ser	gat Asp 1375	tcg Ser	att Ile	gct Ala	gcc Ala	acc Thr 1380	tca Ser	gag Glu	cta Leu	gaa Glu	4508
	aga Arg 1385	aaa Lys	gaa Glu	cac His	gaa Glu	caa Gln 1390	acc Thr	gat Asp	tca Ser	gaa Glu	atc Ile 1395	aag Lys	cag Gln	cta Leu	aag Lys	4553
30	gag Glu 1400	aaa Lys	caa Gln	gat Asp	gtt Val	ttg Leu 1405	caa Gln	aag Lys	tta Leu	ctt Leu	aag Lys 1410	gaa Glu	aaa Lys	gac Asp	ctc Leu	4598
35	tta Leu 1415	atc Ile	aaa Lys	gcc Ala	aaa Lys	agt Ser 1420	gat Asp	caa Gln	cta Leu	ctt Leu	tct Ser 1425	tcc Ser	aat Asn	gaa Glu	aat Asn	4643
	ttc Phe 1430	act Thr	aac Asn	aaa Lys	gta Val	aat Asn 1435	gaa Glu	aac Asn	gaa Glu	ctt Leu	ttg Leu 1440	agg Arg	cag Gln	gca Ala	gta Val	4688
40	aca Thr 1445	aac Asn	ctg Leu	aag Lys	gag Glu	aga Arg 1450	ata Ile	tta Leu	att Ile	cta Leu	gag Glu 1455	atg Met	gac Asp	att Ile	ggc Gly	4733
45	aaa Lys 1460	cta Leu	aaa Lys	gga Gly	gaa Glu	aat Asn 1465	gaa Glu	aaa Lys	ata Ile	gtg Val	gaa Glu 1470	aca Thr	tac Tyr	agg Arg	gga Gly	4778
	aag Lys 1475	gaa Glu	aca Thr	gaa Glu	tat Tyr	caa Gln 1480	gcg Ala	tta Leu	caa Gln	gag Glu	act Thr 1485	aac Asn	atg Met	aag Lys	ttt Phe	4823
50	tct Ser 1490	atg Met	atg Met	ctg Leu	cga Arg	gaa Glu 1495	aaa Lys	gag Glu	ttt Phe	gag Glu	tgc Cys 1500	cac His	tca Ser	atg Met	aag Lys	4868
55	gag Glu 1505	aag Lys	gct Ala	ctt Leu	gct Ala	ttt Phe 1510	gaa Glu	cag Gln	cta Leu	ttg Leu	aaa Lys 1515	gag Glu	aaa Lys	gaa Glu	cag Gln	4913

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	ggc	aag	act	gga	gag	tta	aat	cag	ctt	tta	aat	gca	gtt	aaa	tca	4958
	Gly	Lys	Thr	Gly	Glu	Leu	Asn	Gln	Leu	Leu	Asn	Ala	Val	Lys	Ser	
	1520					1525					1530					
5	atg	cag	gag	aag	aca	gtt	gtg	ttt	caa	cag	gag	aga	gac	caa	gtc	5003
	Met	Gln	Glu	Lys	Thr	Val	Val	Phe	Gln	Gln	Glu	Arg	Asp	Gln	Val	
	1535					1540					1545					
10	atg	ttg	gcc	ctg	aaa	caa	aaa	caa	atg	gaa	aat	act	gcc	cta	cag	5048
	Met	Leu	Ala	Leu	Lys	Gln	Lys	Gln	Met	Glu	Asn	Thr	Ala	Leu	Gln	
	1550					1555					1560					
15	aat	gag	gtt	caa	cgt	tta	cgt	gac	aaa	gaa	ttt	cgt	tca	aac	caa	5093
	Asn	Glu	Val	Gln	Arg	Leu	Arg	Asp	Lys	Glu	Phe	Arg	Ser	Asn	Gln	
	1565					1570					1575					
20	gag	cta	gag	aga	ttg	cgt	aat	cat	ctt	tta	gaa	tca	gaa	gat	tct	5138
	Glu	Leu	Glu	Arg	Leu	Arg	Asn	His	Leu	Leu	Glu	Ser	Glu	Asp	Ser	
	1580					1585					1590					
25	tat	acc	cgt	gaa	gct	ttg	gct	gca	gaa	gat	aga	gag	gct	aaa	cta	5183
	Tyr	Thr	Arg	Glu	Ala	Leu	Ala	Ala	Glu	Asp	Arg	Glu	Ala	Lys	Leu	
	1595					1600					1605					
30	aga	aag	aaa	gtc	aca	gta	ttg	gag	gaa	aag	cta	gtt	tca	tcc	tct	5228
	Arg	Lys	Lys	Val	Thr	Val	Leu	Glu	Glu	Lys	Leu	Val	Ser	Ser	Ser	
	1610					1615					1620					
35	aat	gca	atg	gaa	aat	gca	agc	cat	caa	gcc	agt	gtg	cag	gta	gag	5273
	Asn	Ala	Met	Glu	Asn	Ala	Ser	His	Gln	Ala	Ser	Val	Gln	Val	Glu	
	1625					1630					1635					
40	tca	ttg	caa	gaa	cag	ttg	aat	gta	gtt	tcc	aag	caa	agg	gat	gaa	5318
	Ser	Leu	Gln	Glu	Gln	Leu	Asn	Val	Val	Ser	Lys	Gln	Arg	Asp	Glu	
	1640					1645					1650					
45	act	gcg	ctg	cag	ctt	tct	gtc	tct	cag	gaa	caa	gta	aag	cag	tat	5363
	Thr	Ala	Leu	Gln	Leu	Ser	Val	Ser	Gln	Glu	Gln	Val	Lys	Gln	Tyr	
	1655					1660					1665					
50	gct	ctg	tca	ctg	gcc	aac	ctg	cag	atg	gta	cta	gag	cat	ttc	caa	5408
	Ala	Leu	Ser	Leu	Ala	Asn	Leu	Gln	Met	Val	Leu	Glu	His	Phe	Gln	
	1670					1675					1680					
55	caa	gag	gaa	aaa	gct	atg	tat	tct	gct	gaa	ctc	gaa	aag	caa	aaa	5453
	Gln	Glu	Glu	Lys	Ala	Met	Tyr	Ser	Ala	Glu	Leu	Glu	Lys	Gln	Lys	
	1685					1690					1695					
60	cag	ctt	ata	gct	gaa	tggt	aag	aaa	aac	gca	gaa	aat	ctg	gaa	gga	5498
	Gln	Leu	Ile	Ala	Glu	Trp	Lys	Lys	Asn	Ala	Glu	Asn	Leu	Glu	Gly	
	1700					1705					1710					
65	aaa	gtg	ata	tca	tta	cag	gaa	tgt	ttg	gat	gaa	gca	aat	gct	gca	5543
	Lys	Val	Ile	Ser	Leu	Gln	Glu	Cys	Leu	Asp	Glu	Ala	Asn	Ala	Ala	
	1715					1720					1725					
70	ttg	gat	tca	gca	tca	aga	ctt	aca	gaa	cag	tta	gat	gta	aaa	gaa	5588
	Leu	Asp	Ser	Ala	Ser	Arg	Leu	Thr	Glu	Gln	Leu	Asp	Val	Lys	Glu	
	1730					1735					1740					
75	gaa	caa	att	gaa	gaa	ctt	aaa	aga	caa	aat	gag	ctc	cga	caa	gaa	5633
	Glu	Gln	Ile	Glu	Glu	Leu	Lys	Arg	Gln	Asn	Glu	Leu	Arg	Gln	Glu	
	1745					1750					1755					

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	atg	ctg	gat	gat	gta	caa	aag	aaa	ttg	atg	agc	tta	gca	aac	agc	5678
	Met	Leu	Asp	Asp	Val	Gln	Lys	Lys	Leu	Met	Ser	Leu	Ala	Asn	Ser	
	1760					1765					1770					
5	tca	gaa	gga	aaa	gta	gac	aaa	gtc	cta	atg	aga	aac	ctc	ttc	att	5723
	Ser	Glu	Gly	Lys	Val	Asp	Lys	Val	Leu	Met	Arg	Asn	Leu	Phe	Ile	
	1775					1780					1785					
10	ggt	cat	ttc	cac	aca	ccg	aaa	aat	cag	cgt	cat	gaa	gtg	tta	cgg	5768
	Gly	His	Phe	His	Thr	Pro	Lys	Asn	Gln	Arg	His	Glu	Val	Leu	Arg	
	1790					1795					1800					
15	tta	atg	ggg	agc	atc	ctg	ggc	gtc	aga	agg	gag	gag	atg	gag	cag	5813
	Leu	Met	Gly	Ser	Ile	Leu	Gly	Val	Arg	Arg	Glu	Glu	Met	Glu	Gln	
	1805					1810					1815					
	ttg	ttt	cat	gac	gat	cag	ggc	agt	gtt	acc	agg	tgg	atg	act	ggg	5858
	Leu	Phe	His	Asp	Asp	Gln	Gly	Ser	Val	Thr	Arg	Trp	Met	Thr	Gly	
	1820					1825					1830					
20	tgg	ctt	gga	gga	gga	tca	aaa	agt	gtt	ccc	aac	aca	cct	ttg	aga	5903
	Trp	Leu	Gly	Gly	Gly	Ser	Lys	Ser	Val	Pro	Asn	Thr	Pro	Leu	Arg	
	1835					1840					1845					
25	cca	aat	cag	caa	tct	gtg	gtt	aat	agt	tct	ttt	tca	gaa	ctt	ttt	5948
	Pro	Asn	Gln	Gln	Ser	Val	Val	Asn	Ser	Ser	Phe	Ser	Glu	Leu	Phe	
	1850					1855					1860					
30	gtt	aaa	ttt	cta	gaa	aca	gaa	tct	cat	cca	tcc	att	cca	cca	cca	5993
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	Pro	Arg	Ser	Ala	Ala	Val	Pro	Leu	Ile	Asn	Pro	Ala	Gly	Leu	Gly	
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Phe Thr Lys Asp Met Leu Met Glu Gly Thr Glu Glu Val Glu Ala Glu
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Leu Pro Asp Ser Arg Thr Lys Glu Ile Glu Ala Ile His Ala Ile Leu
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Lys His Glu Ala Ser Glu Ile Gln Ile Lys Gln Gln Ser Thr Ser Tyr
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				260					265					270			
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				740					745					750		
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			755					760					765			
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	785					790					795					800
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					805					810					815	
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					885					890					895	
60	Glu	Val	Ser	Gln	Leu	Asn	Thr	Ile	Lys	Glu	His	Leu	Glu	Glu	Glu	Ile
				900					905					910		
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		930					935					940				
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	945					950					955					960

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		1040					1045					1050					
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		1085					1090					1095					
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	1475						1480					1485			
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	1490						1495					1500			
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Claims

- 30 1. An agent for use in a method of medical treatment, the agent comprising as an effective ingredient any one of the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity, or as an effective ingredient a recombinant vector which comprises a polynucleotide encoding said polypeptide and is capable of expressing said polypeptide *in vivo*:
- 35 (a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING;
(b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and
(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.
- 40 2. The agent according to claim 1, which is for use in a method of inducing immunity.
3. The agent for use according to claim 1 or claim 2, wherein said polypeptide (b) has a homology of not less than 95% to said polypeptide (a).
- 45 4. The agent for use according to claim 1 or claim 2, wherein said polypeptide having an immunity-inducing activity is a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING or a polypeptide comprising said polypeptide as a partial sequence thereof.
- 50 5. The agent for use according to claim 4, wherein said polypeptide having an immunity-inducing activity has the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING.
6. The agent for use according to any one of claims 1 to 5, comprising a polypeptide as an effective ingredient.
- 55 7. The agent for use according to claim 6, which is for use by contacting antigen-presenting cells with the agent *in vitro*, such that the antigen-presenting cells are made to present the polypeptide, and then either (i) administering the antigen-presenting cells to a subject; or (ii) contacting T cells with the antigen-presenting cells *in vitro*, such that cytotoxic T cells specific to the polypeptide are induced and allowed to proliferate, and then administering the

cytotoxic T cells to a subject.

8. The agent for use according to any one of claims 1 to 6, which is for use in the therapeutic and/or prophylactic treatment of a cancer(s).

9. The agent for use according to claim 8, which is for use in humans, dogs or cats.

10. The agent for use according to claim 8 or 9, further comprising an immunoenhancer.

11. The agent for use according to claim 10, wherein said immunoenhancer is at least one selected from the group consisting of Freund's incomplete adjuvant; Montanide; poly I:C and derivatives thereof; CpG oligonucleotides; interleukin-12; interleukin-18; interferon- α ; interferon- β ; interferon- ω ; interferon- γ ; and Flt3 ligand.

12. An *in vitro* method for treating antigen-presenting cells, said method comprising bringing any one of the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity, into contact with antigen-presenting cells:

(a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING;

(b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and

(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

13. An *in vitro* method of preparing a cytotoxic T cell that selectively binds a complex comprising any one of the polypeptides (a) to (c) below, said polypeptide having cytotoxicity-inducing activity of inducing cytotoxic activity against tumor cells in T cells stimulated with the polypeptide, incorporated into an MHC molecule:

(a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING;

(b) a polypeptide having a sequence identity of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and

(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof, the method comprising:

coculturing an antigen-presenting cell prepared according to the method of claim 12 with T cells in a liquid medium, and

allowing the T cells to proliferate.

14. An *in vitro* method according to claim 13, wherein an antigen-presenting cell : T cell ratio of 1:1 to 1:100 is used, optionally wherein the coculture is carried out in the presence of IL-2, IL-6, IL-7 and/or IL-12.

15. An antigen-presenting cell that presents on its surface a complex comprising at least one of the polypeptides (a) to (c) below, said polypeptide having cytotoxicity-inducing activity of inducing cytotoxic activity against tumor cells in T cells stimulated with the polypeptide, incorporated into an MHC molecule:

(a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING;

(b) a polypeptide having a sequence identity of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and

(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

16. An antigen-presenting cell according to claim 15, wherein the antigen presenting cell is a dendritic cell or a B cell.

17. A cytotoxic T cell that selectively binds a complex comprising at least one of the polypeptides (a) to (c) below, said polypeptide having cytotoxicity-inducing activity of inducing cytotoxic activity against tumor cells in T cells stimulated with the polypeptide, incorporated into an MHC molecule:

(a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING;

(b) a polypeptide having a sequence identity of not less than 80% to the polypeptide (a) and consisting of not

less than 7 amino acids; and

(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

5 **18.** The antigen-presenting cell of claim 15 or claim 16, or the cytotoxic T cell of claim 17 for use in a method of medical treatment.

19. The antigen-presenting cell or cytotoxic T cell for use of claim 18, which is for use in the therapeutic and/or prophylactic treatment of a cancer(s).

10 **20.** Use of any one of the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity, or a recombinant vector which comprises a polynucleotide encoding said polypeptide and is capable of expressing said polypeptide in vivo, for production of an agent for use in inducing immunity:

15 (a) a polypeptide consisting of not less than 7 consecutive amino acids of the amino acid sequence shown in SEQ ID NO: 39 or 41 in SEQUENCE LISTING;

 (b) a polypeptide having a homology of not less than 80% to the polypeptide (a) and consisting of not less than 7 amino acids; and

 (c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

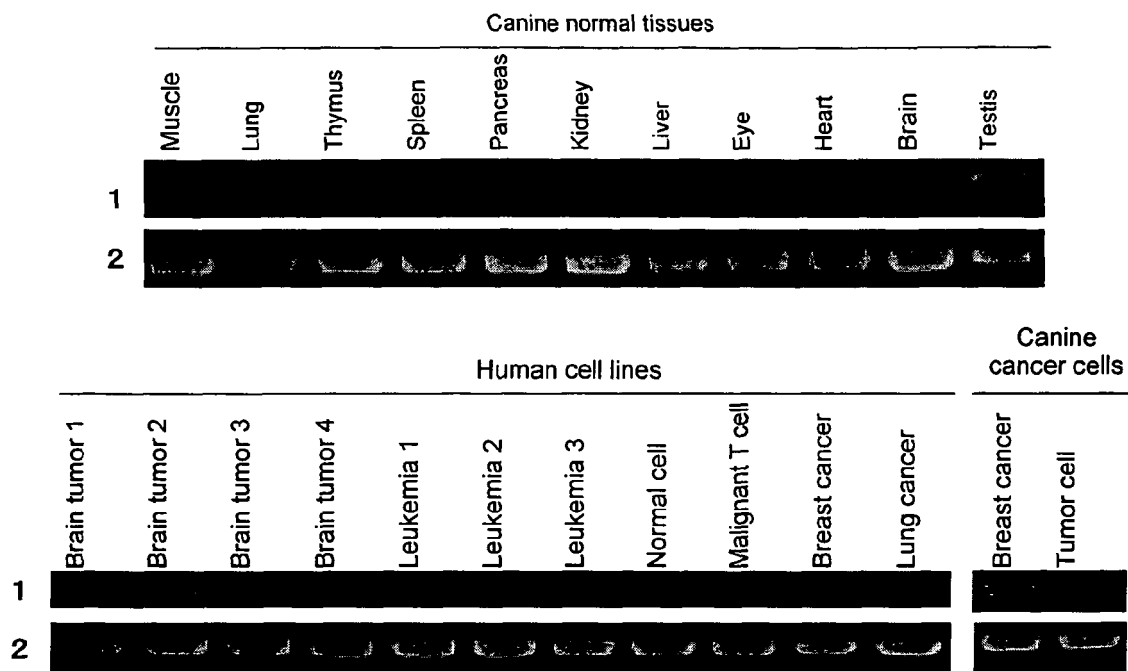


Fig.1

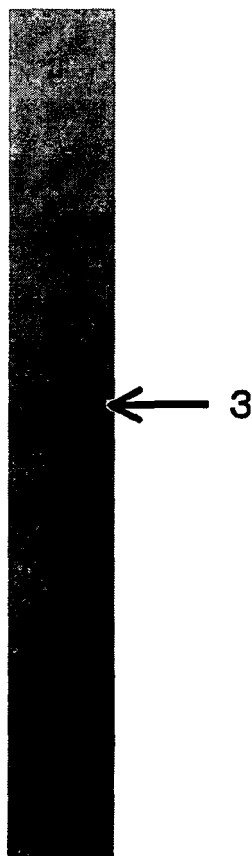


Fig.2

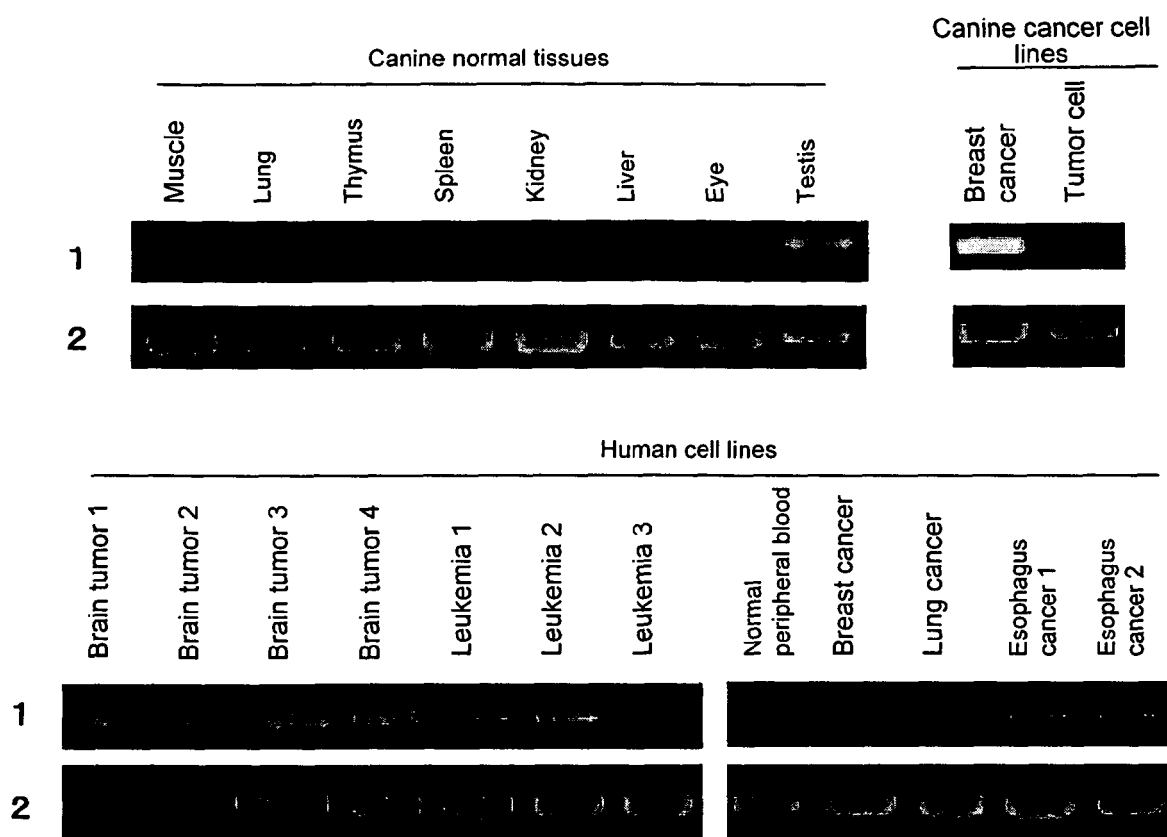


Fig.3

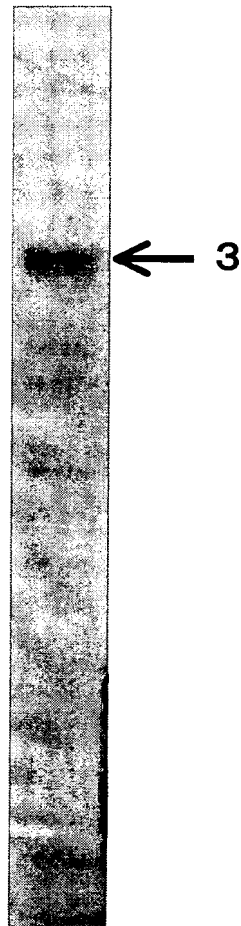


Fig.4

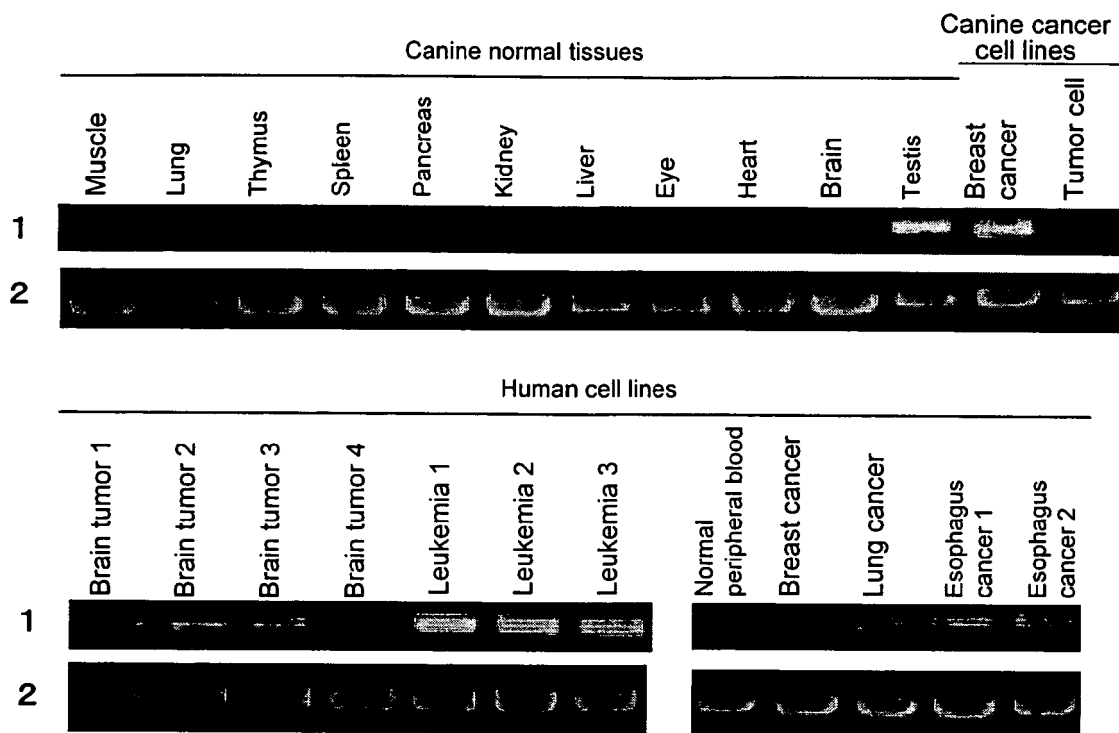


Fig.5

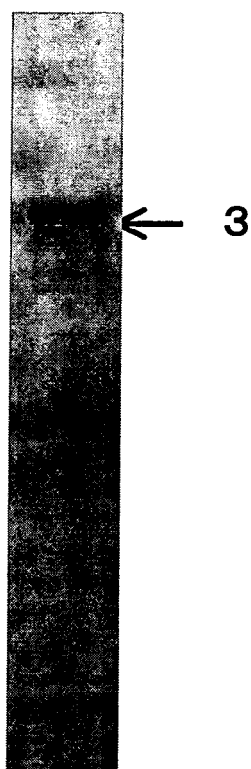


Fig.6

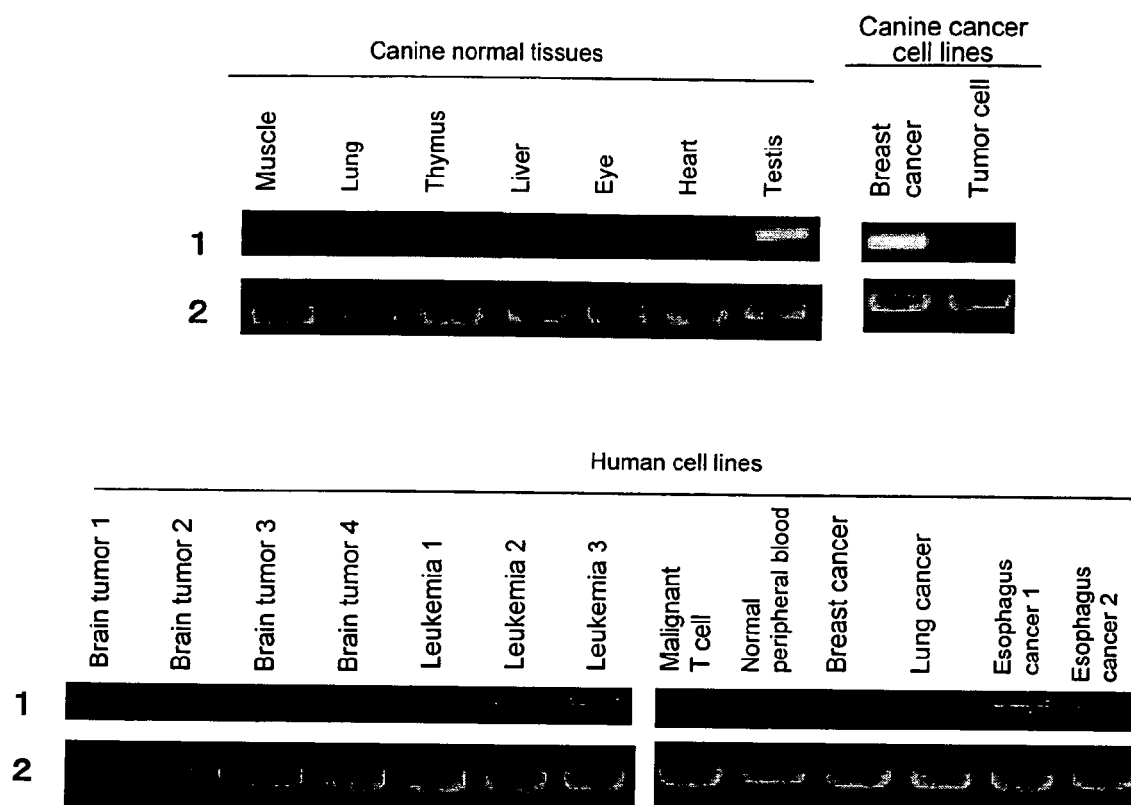


Fig.7

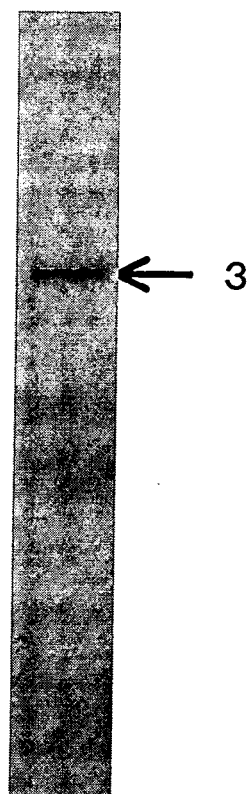


Fig.8



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A	K.-H. CHANG ET AL: "A thyroid hormone receptor coactivator negatively regulated by the retinoblastoma protein", PROCEEDINGS NATIONAL ACADEMY OF SCIENCES PNAS, vol. 94, no. 17, 19 August 1997 (1997-08-19), pages 9040-9045, XP055359897, US ISSN: 0027-8424, DOI: 10.1073/pnas.94.17.9040 * the whole document *	1-20	
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Place of search Munich		Date of completion of the search 3 April 2017	Examiner Cilensek, Zoran
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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Place of search Munich		Date of completion of the search 3 April 2017	Examiner Cilensek, Zoran
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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